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(71) Applicant ( <i>for all designated States except US</i> ): EAST CAROLINA UNIVERSITY [US/US]; 210 Spilman Building, Greenville, NC 27858-4353 (US).  (72) Inventor; and (75) Inventor/Applicant ( <i>for US only</i> ): NYCE, Jonathan, W. [US/US]; 302 Harrell Street, Greenville, NC 27858 (US).  (74) Agents: SIBLEY, Kenneth, D. et al.; Myers Bigel Sibley & Sajovec, P.O. Box 37428, Raleigh, NC 27627 (US).		Published <i>With international search report.</i>	
(54) Title: AGENT AND METHOD OF TREATMENT FOR DISEASES AND CONDITIONS ASSOCIATED WITH RESPIRATORY AILMENTS AND LUNG INFLAMMATION			
(57) Abstract			
<p>An agent comprises anti-sense oligos directed to adenosine receptors for alleviation of respiratory ailments and inflammation. The agent is provided as a composition, various formulations, and kit. The present agents may be administered in an anti-bronchoconstriction and/or anti-inflammation effective amount to alleviate the bronchoconstriction and inflammation afflicting a subject. Preferred agents contain anti-sense oligonucleotide targeting the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and/or A<sub>3</sub> receptors and bradykinin B<sub>2</sub> receptor. The method is useful for treating patients afflicted with asthma and other respiratory problems. Pharmaceutical formulations are also disclosed.</p>			

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**AGENT & METHOD OF TREATMENT FOR DISEASES  
& CONDITIONS ASSOCIATED WITH RESPIRATORY  
AILMENTS & LUNG INFLAMMATION**

**BACKGROUND OF THE INVENTION**

5        This invention was made at least partially with United States Government support under Grant No. ROI-CA47217 from the National Cancer Institute. The United States Government may have certain rights to this invention.

**Field of the Invention**

This invention relates to oligonucleotide agents which are anti-sense to mRNAs  
10 corresponding to genes associated with certain types of lung diseases or conditions. The agents of the invention are effective in the treatment of lung diseases and conditions, such as asthma, and the like, which are associated with lung inflammation, bronchconstriction, impeded air flow through the lung's airways, and general breathing difficulties. Particularly important are agents of the invention comprising oligonucleotides which are anti-sense to the  
15 adenosine A<sub>1</sub>, A<sub>2a</sub> and A<sub>2b</sub> and bradykinin B<sub>2</sub> receptors.

**DESCRIPTION OF THE BACKGROUND**

Respiratory ailments, associated with a variety of diseases and conditions, are extremely common in the general population, and more so in certain ethnic groups, such as black Americans. In some cases "these ailments" are accompanied by inflammation, which  
20 aggravates the condition of the lungs. Asthma, for example, is one of the most common diseases in industrialized countries. In the United States it accounts for about 1% of all health care costs. An alarming increase in both the prevalence and mortality of asthma over the past decade has been reported, and asthma is predicted to be the preeminent occupational lung disease in the next decade. While the increasing mortality of asthma in industrialized  
25 countries could be attributable to the increased reliance upon beta agonists in the treatment of this disease, the underlying causes of asthma remain poorly understood.

Adenosine may constitute an important natural mediator of bronchial asthma. Its potential role in human asthma has been supported by an experimental finding that, in contrast to normal individuals, asthmatic individuals responded to aerosolized adenosine with  
30 marked bronchoconstriction. Similar responses were reported in an experimental rabbit model for human asthma ("the allergic rabbit") produced by administration of the dust mite. Recent work using the allergic rabbit has suggested that bronchoconstriction and bronchial

hyperresponsiveness in asthma may be mediated, at least in part, through the stimulation of adenosine receptors.

The adenosine A<sub>1</sub> receptor appears to be overexpressed in the lungs of virtually every asthma patient, and it has been suggested that sensitivity to adenosine may be a better 5 indicator for asthma than the current standard in the art: the methacholine test. Further evidence of the important role adenosine and its receptors play in asthma is garnered from the observation that adenosine levels are highly elevated in the bronchial lavage fluid of asthmatic lungs. This observation indicates that the overexpressed adenosine A<sub>1</sub> receptor may be subjected to continuous stimulation in the asthmatic lung which, in turn, aggravates 10 bronchoconstriction/inflammation in the asthmatic lung. The overexpressed adenosine A<sub>1</sub> receptor, therefore, may be a fundamental mediator of asthma and other respiratory diseases in which bronchoconstriction and inflammation play a role.

A handful of medicaments have been available for the treatment of respiratory diseases and conditions, although in general they all have limitations. Theophylline, an important drug 15 in the treatment of asthma, is a known adenosine receptor antagonist which was reported to eliminate adenosine-mediated bronchoconstriction in asthmatic rabbits. A selective adenosine A<sub>1</sub> receptor antagonist, 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX) was also reported to inhibit adenosine-mediated bronchoconstriction and bronchial hyperresponsiveness in allergic rabbits. The therapeutic and preventative applications of currently available adenosine A<sub>1</sub>, 20 receptor-specific antagonists are, nevertheless, limited by their toxicity. Theophylline, for example, has been widely used in the treatment of asthma, but is associated with frequent, significant toxicity resulting from its narrow therapeutic dose range. DPCPX is far too toxic to be useful clinically. The fact that despite decades of extensive research, no specific 25 adenosine receptor antagonist is available for clinical use attests to the general toxicity of these agents.

Other adenosine receptors and the bradykinin B<sub>2</sub> receptor are known to be associated with respiratory and inflammatory conditions. Amongst these are the A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> adenosine receptors. The adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> receptors are members of the G-protein coupled family of cell surface receptors having 7-transmembrane segments. There is 30 extensive sequence homology between the A<sub>2a</sub> and A<sub>2b</sub> receptors, with variation occurring primarily in their carboxy terminal domains. The adenosine A<sub>2a</sub> receptor is considered to be a high affinity receptor and the adenosine A<sub>2b</sub> a lower affinity receptor. Whereas the

adenosine A<sub>1</sub> receptor is reported to inhibit adenyl cyclase activity, both A<sub>2a</sub> and A<sub>2b</sub> receptors are reported to stimulate adenyl cyclase activity.

Anti-sense oligonucleotides have received considerable consideration for their potential use as pharmacological agents in human disease. Finding practical and effective 5 applications of these agents in actual models of human disease, however, have been few and far between, particularly because they had to be administered in large doses. Another important consideration in the pharmacologic application of these molecules is their route of administration. Many in vivo applications have involved the direct administration of anti-sense oligonucleotides to limited regions of the brain. Such applications, however, have 10 limited clinical utility due to their invasive nature.

The systemic administration of anti-sense oligonucleotides as pharmacological agents has been found to also have significant problems, not the least of which is a difficulty in targeting disease-involved tissues. That is, the necessary dilution of the anti-sense oligonucleotide in the circulatory system makes it extremely difficult to attain a therapeutic 15 dose at the target tissue by intravenous or oral administration. The bioavailability of orally administered anti-sense oligonucleotides is very low, on the order of less than about 5%.

Accordingly, there is still a need for novel agents which are effective in the treatment of diseases and conditions of the lung that are associated with inflammation and airway obstruction. Of particular importance, for long term preventative and therapeutic applications, 20 are agents which are sufficiently specific, and/or are directly administered to their site of action, to be devoid of undesirable side effects or whose side effects are substantially low to permit their long term administration.

#### SUMMARY OF THE INVENTION

The present invention relates to an agent suitable for reducing bronchoconstriction 25 and/ or lung inflammation which comprises an oligonucleotide which is anti-sense to one or more adenosine, bradykinin and related receptors in the lung. Adenosine and bradykinin receptors which have been associated with these conditions are the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors and bradykinin B<sub>2</sub> receptor. The present agents may be safely administered for the long term prevention, control and therapy of all types of diseases and conditions 30 associated with lung inflammation, bronchoconstriction, airway obstruction and respiratory ailments. The agent of the present invention is also provided as a pharmaceutical

composition, comprising a carrier, preferably a pharmaceutically acceptable carrier, and one or more oligonucleotides which is(are) anti-sense to receptors associated with bronchoconstriction, respiratory problems such as impeded respiration, obstructed airways, mucous buildup and/or lung inflammation, among others. The present agents are also 5 provided as medicament in the form of various formulations for reducing bronchoconstriction and/or inflammation, as well as treating diseases and conditions associated with those symptoms, such as asthma and the like, and as a kit, along with instructions for its administration.

The present agents may be applied to the treatment of ailments which are associated 10 with the described symptoms, including asthma, adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, cystic fibrosis, allergy, emphysema, and the like. The present agents may be administered in an anti-bronchoconstriction and/or anti-inflammatory and/or a respiratory distress alleviating effective amount for either preventative, maintenance or therapeutic applications. Their use 15 is generally indicated for both acute and chronic conditions because of their safety and substantial lack of side effects.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 illustrates the effect of A<sub>1</sub> adenosine receptor anti-sense oligonucleotides and mismatch control anti-sense oligonucleotides on the dynamic compliance of the bronchial 20 airway in a rabbit model. The two stars represent significant difference at p<0.01, Student's t-test.

Figure 2 illustrates the specificity of A<sub>1</sub> adenosine receptor anti-sense oligonucleotides as indicated by the A<sub>1</sub> and A<sub>2</sub> adenosine receptor number present in airway tissue treated with A<sub>1</sub> adenosine receptor anti-sense oligonucleotides.

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#### **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

This invention arose from a desire by the inventor to improve on available prior art technology for the prevention, control and acute and chronic treatment of diseases and conditions which are associated with respiratory difficulties, such as bronchoconstriction, airway obstruction, mucous buildup, allergies, inflammatory responses, and the like. He 30 undertook the search for an agent that could be selectively targeted to specific receptors associated with the observed symptomatology, and at the same time administered to the site

of action. He surmised that the combination of these two strategies would provide a class of medications which are highly effective while resulting in negligible undesirable side effects, which are observed with other agents presently available. He deduced that anti-sense oligonucleotides (oligos) would fulfill these criteria. However, most such anti-sense oligos,  
5 as indicated above, had been administered directly to the brain or systemically, the earlier having limited application in humans, and the latter requiring elevated doses which generally bring about untoward toxicity and/or side effects. Both those classes of drugs are of limited utility, mostly in acute occurrences, whereas their long term administration is contraindicated. In contrast, the inventor postulated that the lung would be an excellent target  
10 for the direct administration of an agent and that, in this manner, he would circumvent a large number of possibilities for interaction of the drug with other tissues and/or fluids which might reasonably be expected to result in a variety of undesired effects. In addition, the inventor contemplated the utilization of anti-sense oligonucleotides to sequences specific to genes and/or messengerRNAs (mRNAs) associated with the conditions or diseases targeted. He thus  
15 set out to pursue the search of oligonucleotides having sequences specific to pre-determined targets which, if hybridized by the oligos, would reduce production of a gene product involved in an undesirable effect, and administered the anti-sense oligos locally, thereby avoiding their dissemination throughout the body of the recipient. Such application represents a non-invasive and tissue-specific approach, never before reported for anti-sense  
20 oligonucleotides.

Nucleotide sequences are presented herein by single strand only, in the 5' to 3' direction, from left to right. Nucleotide and amino acids are represented herein in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission, or (for amino acids) by three letter code, in accordance with 37 CFR § 1.822 and established usage. See,  
25 e.g., Patent In User Manual, 99-102 (Nov. 1990); U.S. Patent and Trademark Office, Office of the Assistant Commissioner for Patents, Washington, DC 20231; US Patent No. 4,871,670 to Hudson et al. at col. 3, lines 20-43, the relevant portions of their disclosure and of all other patents and publications referenced in this patent are incorporated herein by reference.

The method of the present invention may be used to reduce bronchoconstriction and/or  
30 inflammation, particularly adenosine-mediated bronchoconstriction and/or inflammation, of a subject's lungs, resulting from a variety of causes including, but not limited to, asthma, COPD, pulmonary hypertension, allergy and emphysema, among others. Anti-sense

oligonucleotides to the mRNA of the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors and bradykinin B<sub>2</sub> receptor, for example, have been shown by the inventor to be effective in the downregulation of adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and A<sub>3</sub> and bradykinin B<sub>2</sub> receptor molecules, respectively, in the cell. One novel feature of the present agents when compared to more traditional treatments for bronchoconstriction and inflammation, particularly adenosine-mediated and/or bradykinin-mediated respiratory difficulties, bronchoconstriction and/or inflammation, is their ability to specifically target a desired gene product by designing the oligos to be anti-sense to mRNAs encoding a desired product. In one preferred embodiment the agents of the invention are administered directly into the respiration, preferably directly to the lung(s), by inhalation or into the respiratory airways. The present agents, thus, reduce the amount of, for example, a receptor protein itself rather than merely interacting with it, as prior art agents do. In this manner, the mere reduction of the requisite protein intermediary reduces the undesirable symptomatology, e.g., bronchoconstriction, airway obstruction, mucous buildup, significantly reduced respiratory capacity and/or inflammation. The fact that the present agents are specifically targeted rather than generally acting reduces toxicity which results from the generalized interaction of a drug with diverse tissues and receptors.

As used herein, the term "treat" or "treating" a disease or conditions associated with bronchoconstriction, reduced respiratory capacity and/or inflammation, such as is the case in asthma, among others, refers to the administration of the present agents to a subject, preferably directly to the lung or through the respiration or via inhalation, to decrease the likelihood that the subject will manifest symptoms of bronchoconstriction, decreased respiratory capacity or ability and/or inflammation. The term "downregulate" refers to inducing a decrease in inducing production, secretion and/or availability and, thus, a decrease in concentration, of the intracellular level of, for example, adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and/or A<sub>3</sub> and/or bradykinin B<sub>2</sub> receptors. The downregulation of other proteins and/or receptors via inhalation of anti-sense oligonucleotides is also encompassed.

Although the present invention is primarily concerned with the treatment of human subjects it is also intended for the treatment of other vertebrates, including mammalian subjects, such as wild and domesticated animals, farm and marine animals, including horses, 30 zoo animals and pets, e.g. dogs and cats, among other animals. Of particular interest are applications intended for use by a veterinary in the treatment of large and small animals.

The term "anti-sense" generally refers to the use of small, synthetic oligonucleotides,

resembling single-stranded DNA, which are designed to inhibit expression of a specific target gene by inhibiting the function of the corresponding target messenger RNA (mRNA), as described by Milligan et al. See, Milligan, J. F. et al., J. Med. Chem. 36(14), 1923-1937 (1993). The present invention is generally intended to attain the inhibition of the expression 5 of genes associated with bronchoconstriction, inflammation, reduced respiratory ability, and associated symptoms, such as the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and A<sub>3</sub> and bradykinin B<sub>2</sub> receptors. The present agents inhibit gene expression by hybridizing either to the coding (sense), regulatory and/or intron sequences present in the messenger RNA (mRNA) corresponding to the targeted gene. The hybridization or binding of the present agents to fragments of the 10 mRNA target is believed to occur by hydrogen bonding according to Watson-Crick base pairing rules. Although no claim is hereby made to a specific mechanism of action for the present agents, it is presently believed that the exogenously administered anti-sense oligonucleotides decrease the amount of targeted mRNA available for translation and, thereby, decrease the level of the encoded protein and/or cause changes in the growth 15 characteristics or shapes of the cells. Id. See also Helene, C. and Toulme, J., Biochim. Biophys. Acta 1049, 99-125 (1990); Cohen, J. S. D., Ed., Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression; CRC Press: Boca Raton, FL (1987).

"Adenosine receptor anti-sense oligonucleotide" is defined within this patent as a short nucleotide sequence, mostly of synthetic origin, that (1) is complementary to at least a portion 20 of the mRNA, including introns and exon borders corresponding to the 5' and 3' ends, and the intron/exon junction between coding and non-coding regions, and to all segments of the coding and regulatory regions of the mRNA and/or gene which encode the gene product, including the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and A<sub>3</sub> and bradykinin B<sub>2</sub> receptors, and (2) upon hybridization causes a decrease or loss of target mRNA template or template function and/or 25 decreased amounts of the protein encoded by the target mRNA.

The mRNA sequence corresponding to the target gene, e. g. the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> or A<sub>3</sub>, or bradykinin B<sub>2</sub> receptor genes, is generally derived from the DNA base sequence 30 of the gene expressing the target protein which exercises a detrimental role in the disease or condition to be treated. The sequences of all genomic targets exemplified in this patent are in the public domain, and the technology is generally available and widely applied for determining the sequence of any target gene or of its corresponding mRNA so that this technology may easily be applied to other targets. The human A<sub>1</sub> adenosine receptor, for

example, is known and is disclosed in US Patent No. 5,320,962 to Stiles et al. The rat and human adenosine A<sub>3</sub> receptors have been cloned, sequenced and expressed. See, Zhou et al., P.N.A.S. USA 89 :7432 (1992); Jacobson et al., UK Patent Application No. 9304582.1 (1993). The sequence of the adenosine A<sub>2b</sub> gene is known as well. See, Pierce, K.D. et al., 5 Biochem. Biophys. Res. Commun. 187(1):86-93 (1992); Also known is the sequence of the bradykinin B<sub>2</sub> gene. See, Eggerickx, D. et al., Biochem. Biophys. Res. Commun. 187(3):1306-1313 (1992). Thus, anti-sense oligonucleotides that hybridize to mRNA corresponding to the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and A<sub>3</sub>, and bradykinin B<sub>2</sub> genes, and down-regulate the production of the A<sub>1</sub>, A<sub>2b</sub> and/or A<sub>3</sub> receptors may be designed and produced in 10 accordance with standard techniques based on the inventor's teachings provided herein.

This invention, thus, provides an anti-sense oligonucleotide having a sequence selectively binding or hybridizing to any targeted mRNA. Preferred are those oligos that hybridize to any segment of the mRNA which encode the adenosine A<sub>1</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors so as to prevent its translation. In one embodiment of the present invention, the anti-sense 15 oligonucleotide has a sequence selected from the group consisting of SEQ ID NO: 7, and fragments thereof about 8 to about 40 nucleotides long, preferably about 15 to 25 nucleotides long, and more preferably about 18 to 22 nucleotides long starting at different sites of each of the sequences encoding the target genes. Examples of the fragments are provided below, where each one was given a specific fragment number.

20 In another embodiment of the invention, the sequence of the anti-sense oligonucleotide brackets the initiation codon of the human adenosine A<sub>1</sub> receptor. Such an anti-sense oligonucleotide may have a sequence disclosed herein as follows:

5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (SEQ. ID NO: 7)  
25 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 1) (SEQ. ID NO: 11)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 2) (SEQ. ID NO: 12)  
30 5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 3) (SEQ. ID NO: 13)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 4) (SEQ. ID NO: 14)  
5'-C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 5) (SEQ. ID NO: 15)  
35 5'-CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 6) (SEQ. ID NO: 16)  
5'-TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 7) (SEQ. ID NO: 17)  
5'-G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 8) (SEQ. ID NO: 18)  
5'-GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 9) (SEQ. ID NO: 19)  
40 5'-AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 10) (SEQ. ID NO: 20)  
5'-A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 11) (SEQ. ID NO: 21)  
5'-AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 12) (SEQ. ID NO: 22)

5'-GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 13) (SEQ. ID NO: 23)  
 5'-C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 14) (SEQ. ID NO: 24)  
 5'-TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 15) (SEQ. ID NO: 25)  
 5'-GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 16) (SEQ. ID NO: 26)  
 5 5'-A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 17) (SEQ. ID NO: 27)  
 5'-GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 18) (SEQ. ID NO: 28)  
 5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 19) (SEQ. ID NO: 29)  
 5'-T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 20) (SEQ. ID NO: 30)  
 5'-GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 21) (SEQ. ID NO: 31)  
 10 5'-GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 22) (SEQ. ID NO: 32)  
 5'-A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 23) (SEQ. ID NO: 33)  
 5'-GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 24) (SEQ. ID NO: 34)  
 5'-GG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 25) (SEQ. ID NO: 35)  
 5'-G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 26) (SEQ. ID NO: 36)  
 15 5'-CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 27) (SEQ. ID NO: 37)  
 5'-GG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 28) (SEQ. ID NO: 38)  
 5'-G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 29) (SEQ. ID NO: 39)  
 5'-CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 30) (SEQ. ID NO: 40)  
 5'-AT GGC GGG CAC AGG CTG GGC-3' (FRAG 31) (SEQ. ID NO: 41)  
 20 5'-T GGC GGG CAC AGG CTG GGC-3' (FRAG 32) (SEQ. ID NO: 42)  
 5'-GGC GGG CAC AGG CTG GGC-3' (FRAG 33) (SEQ. ID NO: 43)  
 5'-GC GGG CAC AGG CTG GGC-3' (FRAG 34) (SEQ. ID NO: 44)  
 5'-C GGG CAC AGG CTG GGC-3' (FRAG 35) (SEQ. ID NO: 45)  
 5'-GGG CAC AGG CTG GGC-3' (FRAG 36) (SEQ. ID NO: 46)  
 25 5'-GG CAC AGG CTG GGC-3' (FRAG 37) (SEQ. ID NO: 47)  
 5'-G CAC AGG CTG GGC-3' (FRAG 38) (SEQ. ID NO: 48)  
 5'-CAC AGG CTG GGC-3' (FRAG 39) (SEQ. ID NO: 49)  
 5'-AC AGG CTG GGC-3' (FRAG 40) (SEQ. ID NO: 50)  
 5'-C AGG CTG GGC-3' (FRAG 41) (SEQ. ID NO: 51)  
 30 5'-AGG CTG GGC-3' (FRAG 42) (SEQ. ID NO: 52)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 43)  
 (SEQ. ID NO: 53)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 44)  
 (SEQ. ID NO: 54)  
 35 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 45)  
 (SEQ. ID NO: 55)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 46)  
 (SEQ. ID NO: 56)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 47)  
 40 (SEQ. ID NO: 57)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 48)  
 (SEQ. ID NO: 58)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 49) (SEQ. ID NO:  
 59)  
 45 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 50) (SEQ. ID NO: 60)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 51) (SEQ. ID NO: 61)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC -3' (FRAG 52) (SEQ. ID NO: 62)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 53) (SEQ. ID NO: 63)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 54) (SEQ. ID NO: 64)  
 50 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 55) (SEQ. ID NO: 65)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 56) (SEQ. ID NO: 66)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 57) (SEQ. ID NO: 67)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 58) (SEQ. ID NO: 68)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG-3' (FRAG 59) (SEQ. ID NO: 69)  
 55 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G-3' (FRAG 60) (SEQ. ID NO: 70)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 61) (SEQ. ID NO: 71)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 62) (SEQ. ID NO: 72)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 63) (SEQ. ID NO: 73)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 64) (SEQ. ID NO: 74)  
 60 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 65) (SEQ. ID NO: 75)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 66) (SEQ. ID NO: 76)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 67) (SEQ. ID NO: 77)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 68) (SEQ. ID NO: 78)

5'-GGC GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 69) (SEQ. ID NO: 79)  
 5'-GGC GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 70) (SEQ. ID NO: 80)  
 5'-GGC GGC CTG GAA AGC TGA GAT GG -3' (FRAG 71) (SEQ. ID NO: 81)  
 5'-GGC GGC CTG GAA AGC TGA GAT G -3' (FRAG 72) (SEQ. ID NO: 82)  
 5 5'-GGC GGC CTG GAA AGC TGA GAT -3' (FRAG 73) (SEQ. ID NO: 83)  
 5'-GGC GGC CTG GAA AGC TGA GA-3' (FRAG 74) (SEQ. ID NO: 84)  
 5'-GGC GGC CTG GAA AGC TGA G-3' (FRAG 75) (SEQ. ID NO: 85)  
 5'-GGC GGC CTG GAA AGC TGA-3' (FRAG 76) (SEQ. ID NO: 86)  
 5'-GGC GGC CTG GAA AGC TG-3' (FRAG 77) (SEQ. ID NO: 87)  
 10 5'-GGC GGC CTG GAA AGC T -3' (FRAG 78) (SEQ. ID NO: 88)  
 5'-GGC GGC CTG GAA AGC-3' (FRAG 79) (SEQ. ID NO: 89)  
 5'-GGC GGC CTG GAA AG -3' (FRAG 80) (SEQ. ID NO: 90)  
 5'-GGC GGC CTG GAA A-3' (FRAG 81) (SEQ. ID NO: 91)  
 5'-GGC GGC CTG GAA-3' (FRAG 82) (SEQ. ID NO: 92)  
 15 5'-GGC GGC CTG GA-3' (FRAG 83) (SEQ. ID NO: 93)  
 5'-GGC GGC CTG G-3' (FRAG 84) (SEQ. ID NO: 94)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 85)  
 (SEQ. ID NO: 95)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 86)  
 20 (SEQ. ID NO: 96)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 87)  
 (SEQ. ID NO: 97)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 88)  
 (SEQ. ID NO: 98)  
 25 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 89)  
 (SEQ. ID NO: 99)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 90) (SEQ. ID NO:  
 100)

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30 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 91) (SEQ. ID NO: 101)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 92) (SEQ. ID NO: 102)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 93) (SEQ. ID NO: 103)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC -3' (FRAG 94) (SEQ. ID NO: 104)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 95) (SEQ. ID NO: 105)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 96) (SEQ. ID NO: 106)  
 35 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 97) (SEQ. ID NO: 107)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 98) (SEQ. ID NO: 108)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 99) (SEQ. ID NO: 109)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 100) (SEQ. ID NO: 110)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 101) (SEQ. ID NO: 111)  
 40 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 102) (SEQ. ID NO: 112)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 103) (SEQ. ID NO: 113)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 104) (SEQ. ID NO: 114)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 105) (SEQ. ID NO: 115)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 106) (SEQ. ID NO: 116)  
 45 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 107) (SEQ. ID NO: 117)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 108) (SEQ. ID NO: 118)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 109) (SEQ. ID NO: 119)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 110) (SEQ. ID NO: 120)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 111) (SEQ. ID NO: 121)  
 50 5'-GC GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 112) (SEQ. ID NO: 122)  
 5'-GC GGC CTG GAA AGC TGA GAT GG -3' (FRAG 113) (SEQ. ID NO: 123)  
 5'-GC GGC CTG GAA AGC TGA GAT G -3' (FRAG 114) (SEQ. ID NO: 124)  
 5'-GC GGC CTG GAA AGC TGA GAT -3' (FRAG 115) (SEQ. ID NO: 125)  
 5'-GC GGC CTG GAA AGC TGA GA-3' (FRAG 116) (SEQ. ID NO: 126)  
 55 5'-GC GGC CTG GAA AGC TGA G-3' (FRAG 117) (SEQ. ID NO: 127)  
 5'-GC GGC CTG GAA AGC TGA-3' (FRAG 118) (SEQ. ID NO: 128)  
 5'-GC GGC CTG GAA AGC TG-3' (FRAG 119) (SEQ. ID NO: 129)  
 5'-GC GGC CTG GAA AGC T -3' (FRAG 120) (SEQ. ID NO: 130)  
 5'-GC GGC CTG GAA AGC-3' (FRAG 121) (SEQ. ID NO: 131)  
 60 5'-GC GGC CTG GAA AG-3' (FRAG 122) (SEQ. ID NO: 132)  
 5'-GC GGC CTG GAA A-3' (FRAG 123) (SEQ. ID NO: 133)  
 5'-GC GGC CTG GAA-3' (FRAG 124) (SEQ. ID NO: 134)  
 5'-GC GGC CTG GA-3' (FRAG 125) (SEQ. ID NO: 135)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 126)  
 (SEQ. ID NO: 136)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 127)  
 (SEQ. ID NO: 137)

5 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 128)  
 (SEQ. ID NO: 138)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 129)  
 (SEQ. ID NO: 139)

10 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 130)  
 (SEQ. ID NO: 140)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 131) (SEQ. ID NO:  
 141)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 132) (SEQ. ID NO: 142)

15 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 133) (SEQ. ID NO: 143)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 134) (SEQ. ID NO: 144)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 135) (SEQ. ID NO: 145)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 136) (SEQ. ID NO: 146)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 137) (SEQ. ID NO: 147)

20 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 138) (SEQ. ID NO: 148)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 139) (SEQ. ID NO: 149)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 140) (SEQ. ID NO: 150)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 141) (SEQ. ID NO: 151)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG-3' (FRAG 142) (SEQ. ID NO: 152)

25 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G-3' (FRAG 143) (SEQ. ID NO: 153)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 144) (SEQ. ID NO: 154)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 145) (SEQ. ID NO: 155)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 146) (SEQ. ID NO: 156)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 147) (SEQ. ID NO: 157)

30 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 148) (SEQ. ID NO: 158)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 149) (SEQ. ID NO: 159)

5'-C GGC CTG GAA AGC TGA GAT GGA GGG G -3' (FRAG 150) (SEQ. ID NO: 160)

5'-C GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 151) (SEQ. ID NO: 161)

5'-C GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 152) (SEQ. ID NO: 162)

5'-C GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 153) (SEQ. ID NO: 163)

35 5'-C GGC CTG GAA AGC TGA GAT GG -3' (FRAG 154) (SEQ. ID NO: 164)

5'-C GGC CTG GAA AGC TGA GAT G -3' (FRAG 155) (SEQ. ID NO: 165)

5'-C GGC CTG GAA AGC TGA GAT -3' (FRAG 156) (SEQ. ID NO: 166)

5'-C GGC CTG GAA AGC TGA GA-3' (FRAG 157) (SEQ. ID NO: 167)

5'-C GGC CTG GAA AGC TGA G-3' (FRAG 158) (SEQ. ID NO: 168)

40 5'-C GGC CTG GAA AGC TGA-3' (FRAG 159) (SEQ. ID NO: 169)

5'-C GGC CTG GAA AGC TG-3' (FRAG 160) (SEQ. ID NO: 170)

5'-C GGC CTG GAA AGC T-3' (FRAG 161) (SEQ. ID NO: 171)

5'-C GGC CTG GAA AGC -3' (FRAG 162) (SEQ. ID NO: 172)

5'-C GGC CTG GAA AG-3' (FRAG 163) (SEQ. ID NO: 173)

45 5'-C GGC CTG GAA A-3' (FRAG 164) (SEQ. ID NO: 174)

5'-C GGC CTG GAA-3' (FRAG 165) (SEQ. ID NO: 175)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 166)  
 (SEQ. ID NO: 176)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 167)  
 (SEQ. ID NO: 177)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 168)  
 (SEQ. ID NO: 178)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 169)  
 (SEQ. ID NO: 179)

55 5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 170) (SEQ. ID NO:  
 180)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 171) (SEQ. ID NO: 181)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 172) (SEQ. ID NO: 182)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 173) (SEQ. ID NO: 183)

60 5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 174) (SEQ. ID NO: 184)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 175) (SEQ. ID NO: 185)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 176) (SEQ. ID NO: 186)

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 177) (SEQ. ID NO: 187)

- 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 178) (SEQ. ID NO: 188)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 179) (SEQ. ID NO: 189)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 180) (SEQ. ID NO: 190)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 181) (SEQ. ID NO: 191)  
 5 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 182) (SEQ. ID NO: 192)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 183) (SEQ. ID NO: 193)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 184) (SEQ. ID NO: 194)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 185) (SEQ. ID NO: 195)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 186) (SEQ. ID NO: 196)
- 10 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 187) (SEQ. ID NO: 197)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 188) (SEQ. ID NO: 198)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 189) (SEQ. ID NO: 199)  
 5'- GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 190) (SEQ. ID NO: 200)  
 5'- GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 191) (SEQ. ID NO: 201)
- 15 5'- GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 192) (SEQ. ID NO: 202)  
 5'- GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 193) (SEQ. ID NO: 203)  
 5'- GGC CTG GAA AGC TGA GAT GG -3' (FRAG 194) (SEQ. ID NO: 204)  
 5'- GGC CTG GAA AGC TGA GAT G -3' (FRAG 195) (SEQ. ID NO: 205)  
 5'- GGC CTG GAA AGC TGA GAT -3' (FRAG 196) (SEQ. ID NO: 206)
- 20 5'- GGC CTG GAA AGC TGA GA-3' (FRAG 197) (SEQ. ID NO: 207)  
 5'- GGC CTG GAA AGC TGA G-3' (FRAG 198) (SEQ. ID NO: 208)  
 5'- GGC CTG GAA AGC TGA-3' (FRAG 199) (SEQ. ID NO: 209)  
 5'- GGC CTG GAA AGC TG-3' (FRAG 200) (SEQ. ID NO: 210)  
 5'- GGC CTG GAA AGC T-3' (FRAG 201) (SEQ. ID NO: 211)
- 25 5'- GGC CTG GAA AGC-3' (FRAG 202) (SEQ. ID NO: 212)  
 5'- GGC CTG GAA AG-3' (FRAG 203) (SEQ. ID NO: 213)  
 5'- GGC CTG GAA A-3' (FRAG 204) (SEQ. ID NO: 214)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 205)  
 (SEQ. ID NO: 215)
- 30 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 206)  
 (SEQ. ID NO: 216)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 207)  
 (SEQ. ID NO: 217)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 208) (SEQ. ID NO:  
 35 218)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 209) (SEQ. ID NO: 219)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 210) (SEQ. ID NO: 220)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 211) (SEQ. ID NO: 221)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 212) (SEQ. ID NO: 222)
- 40 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 213) (SEQ. ID NO: 223)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 214) (SEQ. ID NO: 224)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 215) (SEQ. ID NO: 225)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 216) (SEQ. ID NO: 226)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 217) (SEQ. ID NO: 227)
- 45 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 218) (SEQ. ID NO: 228)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 219) (SEQ. ID NO: 229)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 220) (SEQ. ID NO: 230)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 221) (SEQ. ID NO: 231)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 222) (SEQ. ID NO: 232)
- 50 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 223) (SEQ. ID NO: 233)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 224) (SEQ. ID NO: 234)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 225) (SEQ. ID NO: 235)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 226) (SEQ. ID NO: 236)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 227) (SEQ. ID NO: 237)
- 55 5'- GC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 228) (SEQ. ID NO: 238)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 229) (SEQ. ID NO: 239)  
 5'- GC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 230) (SEQ. ID NO: 240)  
 5'- GC CTG GAA AGC TGA GAT GGA G -3' (FRAG 231) (SEQ. ID NO: 241)  
 5'- GC CTG GAA AGC TGA GAT GGA G -3' (FRAG 232) (SEQ. ID NO: 242)
- 60 60 5'- GC CTG GAA AGC TGA GAT GG -3' (FRAG 233) (SEQ. ID NO: 243)  
 5'- GC CTG GAA AGC TGA GAT G -3' (FRAG 234) (SEQ. ID NO: 244)  
 5'- GC CTG GAA AGC TGA GAT -3' (FRAG 235) (SEQ. ID NO: 245)  
 5'- GC CTG GAA AGC TGA GA-3' (FRAG 236) (SEQ. ID NO: 246)

5'- GC CTG GAA AGC TGA G-3' (FRAG 237) (SEQ. ID NO: 247)  
 5'- GC CTG GAA AGC TGA-3' (FRAG 238) (SEQ. ID NO: 248)  
 5'- GC CTG GAA AGC TG-3' (FRAG 239) (SEQ. ID NO: 249)  
 5'- GC CTG GAA AGC T-3' (FRAG 240) (SEQ. ID NO: 250)  
 5 5'- GC CTG GAA AGC-3' (FRAG 241) (SEQ. ID NO: 251)  
 5'- GC CTG GAA AG-3' (FRAG 242) (SEQ. ID NO: 252)  
 5'- C CTG GAA AGC TGA GAT GG A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 243)  
 (SEQ. ID NO: 253)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 244)  
 10 (SEQ. ID NO: 254)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 245) (SEQ. ID NO:  
 255)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 246) (SEQ. ID NO: 256)  
 15 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 247) (SEQ. ID NO: 257)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 248) (SEQ. ID NO: 258)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 249) (SEQ. ID NO: 259)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 250) (SEQ. ID NO: 260)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 251) (SEQ. ID NO: 261)  
 20 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 252) (SEQ. ID NO: 262)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 253) (SEQ. ID NO: 263)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 254) (SEQ. ID NO: 264)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 255) (SEQ. ID NO: 265)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 256) (SEQ. ID NO: 266)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 257) (SEQ. ID NO: 267)  
 25 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 258) (SEQ. ID NO: 268)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 259) (SEQ. ID NO: 269)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 260) (SEQ. ID NO: 270)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 261) (SEQ. ID NO: 271)  
 30 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 262) (SEQ. ID NO: 272)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 263) (SEQ. ID NO: 273)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 264) (SEQ. ID NO: 274)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 265) (SEQ. ID NO: 275)  
 5'- C CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 266) (SEQ. ID NO: 276)  
 5'- C CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 267) (SEQ. ID NO: 277)  
 35 5'- C CTG GAA AGC TGA GAT GGA GG -3' (FRAG 268) (SEQ. ID NO: 278)  
 5'- C CTG GAA AGC TGA GAT GGA G -3' (FRAG 269) (SEQ. ID NO: 279)  
 5'- C CTG GAA AGC TGA GAT GGA -3' (FRAG 270) (SEQ. ID NO: 280)  
 5'- C CTG GAA AGC TGA GAT GG -3' (FRAG 271) (SEQ. ID NO: 281)  
 5'- C CTG GAA AGC TGA GAT G -3' (FRAG 272) (SEQ. ID NO: 282)  
 40 5'- C CTG GAA AGC TGA GAT -3' (FRAG 273) (SEQ. ID NO: 283)  
 5'- C CTG GAA AGC TGA GA-3' (FRAG 274) (SEQ. ID NO: 284)  
 5'- C CTG GAA AGC TGA G-3' (FRAG 275) (SEQ. ID NO: 285)  
 5'- C CTG GAA AGC TGA-3' (FRAG 276) (SEQ. ID NO: 286)  
 5'- C CTG GAA AGC TG-3' (FRAG 277) (SEQ. ID NO: 287)  
 45 5'- C CTG GAA AGC T-3' (FRAG 278) (SEQ. ID NO: 288)  
 5'- C CTG GAA AGC-3' (FRAG 279) (SEQ. ID NO: 289)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 280) (SEQ. ID NO:  
 290)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 281) (SEQ. ID NO:  
 291)  
 50 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 282) (SEQ. ID NO:  
 292)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 283) (SEQ. ID NO: 293)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 284) (SEQ. ID NO: 294)  
 55 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 285) (SEQ. ID NO: 295)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 286) (SEQ. ID NO: 296)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 287) (SEQ. ID NO: 297)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 288) (SEQ. ID NO: 298)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 289) (SEQ. ID NO: 299)  
 60 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 290) (SEQ. ID NO: 300)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 291) (SEQ. ID NO: 301)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 292) (SEQ. ID NO: 302)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 293) (SEQ. ID NO: 303)

- 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 294) (SEQ. ID NO: 304)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 295) (SEQ. ID NO: 305)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 296) (SEQ. ID NO: 306)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 297) (SEQ. ID NO: 307)  
 5 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 298) (SEQ. ID NO: 308)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 299) (SEQ. ID NO: 309)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 300) (SEQ. ID NO: 310)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 301) (SEQ. ID NO: 311)  
 5'- CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 302) (SEQ. ID NO: 312)  
 10 5'- CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 303) (SEQ. ID NO: 313)  
 5'- CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 304) (SEQ. ID NO: 314)  
 5'- CTG GAA AGC TGA GAT GGA GG -3' (FRAG 305) (SEQ. ID NO: 315)  
 5'- CTG GAA AGC TGA GAT GGA G -3' (FRAG 306) (SEQ. ID NO: 316)  
 5'- CTG GAA AGC TGA GAT GGA -3' (FRAG 307) (SEQ. ID NO: 317)  
 15 5'- CTG GAA AGC TGA GAT GG -3' (FRAG 308) (SEQ. ID NO: 318)  
 5'- CTG GAA AGC TGA GAT G -3' (FRAG 309) (SEQ. ID NO: 319)  
 5'- CTG GAA AGC TGA GAT -3' (FRAG 310) (SEQ. ID NO: 320)  
 5'- CTG GAA AGC TGA GA-3' (FRAG 311) (SEQ. ID NO: 321)  
 5'- CTG GAA AGC TGA G -3' (FRAG 312) (SEQ. ID NO: 322)  
 20 5'- CTG GAA AGC TGA-3' (FRAG 313) (SEQ. ID NO: 323)  
 5'- CTG GAA AGC TG-3' (FRAG 314) (SEQ. ID NO: 324)  
 5'- CTG GAA AGC T-3' (FRAG 315) (SEQ. ID NO: 325)  
  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 316) (SEQ. ID NO:  
 326)  
 25 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 317) (SEQ. ID NO:  
 327)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 318) (SEQ. ID NO: 328)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 319) (SEQ. ID NO: 329)  
 30 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT -3' (FRAG 320) (SEQ. ID NO: 330)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C -3' (FRAG 321) (SEQ. ID NO: 331)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 322) (SEQ. ID NO: 332)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 323) (SEQ. ID NO: 333)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 324) (SEQ. ID NO: 334)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 325) (SEQ. ID NO: 335)  
 35 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 326) (SEQ. ID NO: 336)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 327) (SEQ. ID NO: 337)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 328) (SEQ. ID NO: 338)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 329) (SEQ. ID NO: 339)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 330) (SEQ. ID NO: 340)  
 40 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 331) (SEQ. ID NO: 341)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 332) (SEQ. ID NO: 342)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 333) (SEQ. ID NO: 343)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 334) (SEQ. ID NO: 344)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 335) (SEQ. ID NO: 345)  
 45 5'- TG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 336) (SEQ. ID NO: 346)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 337) (SEQ. ID NO: 347)  
 5'- TG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 338) (SEQ. ID NO: 348)  
 5'- TG GAA AGC TGA GAT GGA GGG C -3' (FRAG 339) (SEQ. ID NO: 349)  
 5'- TG GAA AGC TGA GAT GGA GG -3' (FRAG 340) (SEQ. ID NO: 350)  
 50 5'- TG GAA AGC TGA GAT GGA GG -3' (FRAG 341) (SEQ. ID NO: 351)  
 5'- TG GAA AGC TGA GAT GGA G -3' (FRAG 342) (SEQ. ID NO: 352)  
 5'- TG GAA AGC TGA GAT GGA -3' (FRAG 343) (SEQ. ID NO: 353)  
 5'- TG GAA AGC TGA GAT GG -3' (FRAG 344) (SEQ. ID NO: 354)  
 5'- TG GAA AGC TGA GAT G -3' (FRAG 345) (SEQ. ID NO: 355)  
 55 5'- TG GAA AGC TGA GAT -3' (FRAG 346) (SEQ. ID NO: 356)  
 5'- TG GAA AGC TGA GA-3' (FRAG 347) (SEQ. ID NO: 357)  
 5'- TG GAA AGC TGA G-3' (FRAG 348) (SEQ. ID NO: 358)  
 5'- TG GAA AGC TGA-3' (FRAG 349) (SEQ. ID NO: 359)  
 5'- TG GAA AGC TG-3' (FRAG 350) (SEQ. ID NO: 360)  
 60 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 351) (SEQ. ID NO:  
 361)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 352) (SEQ. ID NO: 362)

5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 353) (SEQ. ID NO: 363)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 354) (SEQ. ID NO: 364)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 355) (SEQ. ID NO: 365)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 356) (SEQ. ID NO: 366)  
 5 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 357) (SEQ. ID NO: 367)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 358) (SEQ. ID NO: 368)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 359) (SEQ. ID NO: 369)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 360) (SEQ. ID NO: 370)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 361) (SEQ. ID NO: 371)  
 10 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 362) (SEQ. ID NO: 372)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 363) (SEQ. ID NO: 373)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 364) (SEQ. ID NO: 374)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 365) (SEQ. ID NO: 375)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 366) (SEQ. ID NO: 376)  
 15 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 367) (SEQ. ID NO: 377)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 368) (SEQ. ID NO: 378)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 369) (SEQ. ID NO: 379)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 370) (SEQ. ID NO: 380)  
 5'- G GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 371) (SEQ. ID NO: 381)  
 20 5'- G GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 372) (SEQ. ID NO: 382)  
 5'- G GAA AGC TGA GAT GGA GGG CG -3' (FRAG 373) (SEQ. ID NO: 383)  
 5'- G GAA AGC TGA GAT GGA GGG C -3' (FRAG 374) (SEQ. ID NO: 384)  
 5'- G GAA AGC TGA GAT GGA GGG -3' (FRAG 375) (SEQ. ID NO: 385)  
 5'- G GAA AGC TGA GAT GGA GG -3' (FRAG 376) (SEQ. ID NO: 386)  
 25 5'- G GAA AGC TGA GAT GGA G -3' (FRAG 377) (SEQ. ID NO: 387)  
 5'- G GAA AGC TGA GAT GGA -3' (FRAG 378) (SEQ. ID NO: 388)  
 5'- G GAA AGC TGA GAT GG -3' (FRAG 379) (SEQ. ID NO: 389)  
 5'- G GAA AGC TGA GAT G -3' (FRAG 380) (SEQ. ID NO: 390)  
 5'- G GAA AGC TGA GAT -3' (FRAG 381) (SEQ. ID NO: 391)  
 30 5'- G GAA AGC TGA GA-3' (FRAG 382) (SEQ. ID NO: 392)  
 5'- G GAA AGC TGA G-3' (FRAG 383) (SEQ. ID NO: 393)  
 5'- G GAA AGC TGA A-3' (FRAG 384) (SEQ. ID NO: 394)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 385) (SEQ. ID NO: 395)  
 35 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 386) (SEQ. ID NO: 396)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 387) (SEQ. ID NO: 397)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 388) (SEQ. ID NO: 398)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 389) (SEQ. ID NO: 399)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 390) (SEQ. ID NO: 400)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 391) (SEQ. ID NO: 401)  
 40 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 392) (SEQ. ID NO: 402)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 393) (SEQ. ID NO: 403)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 394) (SEQ. ID NO: 404)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 395) (SEQ. ID NO: 405)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 396) (SEQ. ID NO: 406)  
 45 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 397) (SEQ. ID NO: 407)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 398) (SEQ. ID NO: 408)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 399) (SEQ. ID NO: 409)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 400) (SEQ. ID NO: 410)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 401) (SEQ. ID NO: 411)  
 50 5'- GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 402) (SEQ. ID NO: 412)  
 5'- GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 403) (SEQ. ID NO: 413)  
 5'- GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 404) (SEQ. ID NO: 414)  
 5'- GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 405) (SEQ. ID NO: 415)  
 5'- GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 406) (SEQ. ID NO: 416)  
 55 5'- GAA AGC TGA GAT GGA GGG CG -3' (FRAG 407) (SEQ. ID NO: 417)  
 5'- GAA AGC TGA GAT GGA GGG C -3' (FRAG 408) (SEQ. ID NO: 418)  
 5'- GAA AGC TGA GAT GGA GGG -3' (FRAG 409) (SEQ. ID NO: 419)  
 5'- GAA AGC TGA GAT GGA GG -3' (FRAG 410) (SEQ. ID NO: 420)  
 5'- GAA AGC TGA GAT GGA G -3' (FRAG 411) (SEQ. ID NO: 421)  
 60 5'- GAA AGC TGA GAT GGA A -3' (FRAG 412) (SEQ. ID NO: 422)  
 5'- GAA AGC TGA GAT GG -3' (FRAG 413) (SEQ. ID NO: 423)  
 5'- GAA AGC TGA GAT G -3' (FRAG 414) (SEQ. ID NO: 424)  
 5'- GAA AGC TGA GAT -3' (FRAG 415) (SEQ. ID NO: 425)

- 5'- GAA AGC TGA GA-3' (FRAG 416) (SEQ. ID NO: 426)  
 5'- GAA AGC TGA G-3' (FRAG 417) (SEQ. ID NO: 427)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 418) (SEQ. ID NO: 428)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 419) (SEQ. ID NO: 429)
- 5 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 420) (SEQ. ID NO: 430)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 421) (SEQ. ID NO: 431)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 422) (SEQ. ID NO: 432)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 423) (SEQ. ID NO: 433)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3'(FRAG 424) (SEQ. ID NO: 434)
- 10 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 425) (SEQ. ID NO: 435)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 426) (SEQ. ID NO: 436)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 427) (SEQ. ID NO: 437)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 428) (SEQ. ID NO: 438)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 429) (SEQ. ID NO: 439)
- 15 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 430) (SEQ. ID NO: 440)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 431) (SEQ. ID NO: 441)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 432) (SEQ. ID NO: 442)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 433) (SEQ. ID NO: 443)
- 20 5'- AA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 434) (SEQ. ID NO: 444)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 435) (SEQ. ID NO: 445)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 436) (SEQ. ID NO: 446)  
 5'- AA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 437) (SEQ. ID NO: 447)  
 5'- AA AGC TGA GAT GGA GGG CGG C-3' (FRAG 438) (SEQ. ID NO: 448)
- 25 5'- AA AGC TGA GAT GGA GGG CGG -3' (FRAG 439) (SEQ. ID NO: 449)  
 5'- AA AGC TGA GAT GGA GGG CG -3' (FRAG 440) (SEQ. ID NO: 450)  
 5'- AA AGC TGA GAT GGA GGG C -3' (FRAG 441) (SEQ. ID NO: 451)  
 5'- AA AGC TGA GAT GGA GGG -3' (FRAG 442) (SEQ. ID NO: 452)  
 5'- AA AGC TGA GAT GGA GG -3' (FRAG 443) (SEQ. ID NO: 453)
- 30 5'- AA AGC TGA GAT GGA G -3' (FRAG 444) (SEQ. ID NO: 454)  
 5'- AA AGC TGA GAT GGA -3' (FRAG 445) (SEQ. ID NO: 455)  
 5'- AA AGC TGA GAT GG -3' (FRAG 446) (SEQ. ID NO: 456)  
 5'- AA AGC TGA GAT G -3' (FRAG 447) (SEQ. ID NO: 457)  
 5'- AA AGC TGA GAT -3' (FRAG 448) (SEQ. ID NO: 458)  
 5'- AA AGC TGA GA-3' (FRAG 449) (SEQ. ID NO: 459)
- 35 5'- A AGC TGA GAT GGA GGG CG G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 450) (SEQ. ID NO: 460)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 451) (SEQ. ID NO: 461)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 452) (SEQ. ID NO: 462)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 453) (SEQ. ID NO: 463)
- 40 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 454) (SEQ. ID NO: 464)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 455) (SEQ. ID NO: 465)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 456) (SEQ. ID NO: 466)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 457) (SEQ. ID NO: 467)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 458) (SEQ. ID NO: 468)
- 45 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 459) (SEQ. ID NO: 469)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 460) (SEQ. ID NO: 470)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 461) (SEQ. ID NO: 471)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 462) (SEQ. ID NO: 472)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 463) (SEQ. ID NO: 473)
- 50 5'- A AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 464) (SEQ. ID NO: 474)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 465) (SEQ. ID NO: 475)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 466) (SEQ. ID NO: 476)  
 5'- A AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 467) (SEQ. ID NO: 477)  
 5'- A AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 468) (SEQ. ID NO: 478)
- 55 5'- A AGC TGA GAT GGA GGG CGG CA-3' (FRAG 469) (SEQ. ID NO: 479)  
 5'- A AGC TGA GAT GGA GGG CGG C-3' (FRAG 470) (SEQ. ID NO: 480)  
 5'- A AGC TGA GAT GGA GGG CGG -3' (FRAG 471) (SEQ. ID NO: 481)  
 5'- A AGC TGA GAT GGA GGG CG -3' (FRAG 472) (SEQ. ID NO: 482)  
 5'- A AGC TGA GAT GGA GGG C -3' (FRAG 473) (SEQ. ID NO: 483)
- 60 5'- A AGC TGA GAT GGA GGG -3' (FRAG 474) (SEQ. ID NO: 484)  
 5'- A AGC TGA GAT GGA GG -3' (FRAG 475) (SEQ. ID NO: 485)  
 5'- A AGC TGA GAT GGA G -3' (FRAG 476) (SEQ. ID NO: 486)  
 5'- A AGC TGA GAT GGA -3' (FRAG 477) (SEQ. ID NO: 487)  
 5'- A AGC TGA GAT GG -3' (FRAG 478) (SEQ. ID NO: 488)

- 5'- A AGC TGA GAT G -3' (FRAG 479) (SEQ. ID NO: 489)  
 5'- A AGC TGA GAT -3' (FRAG 480) (SEQ. ID NO: 490)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 481) (SEQ. ID NO: 491)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 482) (SEQ. ID NO: 492)
- 5 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 483) (SEQ. ID NO: 493)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 484) (SEQ. ID NO: 494)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT -3' (FRAG 485) (SEQ. ID NO: 495)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 486) (SEQ. ID NO: 496)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 487) (SEQ. ID NO: 497)
- 10 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 488) (SEQ. ID NO: 498)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 489) (SEQ. ID NO: 499)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 490) (SEQ. ID NO: 500)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 491) (SEQ. ID NO: 501)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 492) (SEQ. ID NO: 502)
- 15 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 493) (SEQ. ID NO: 503)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 494) (SEQ. ID NO: 504)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 495) (SEQ. ID NO: 505)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 496) (SEQ. ID NO: 506)  
 5'- AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 497) (SEQ. ID NO: 507)
- 20 5'- AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 498) (SEQ. ID NO: 508)  
 5'- AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 499) (SEQ. ID NO: 509)  
 5'- AGC TGA GAT GGA GGG CGG CA-3' (FRAG 500) (SEQ. ID NO: 510)  
 5'- AGC TGA GAT GGA GGG CGG C-3' (FRAG 501) (SEQ. ID NO: 511)  
 5'- AGC TGA GAT GGA GGG CGG -3' (FRAG 502) (SEQ. ID NO: 512)
- 25 5'- AGC TGA GAT GGA GGG CG -3' (FRAG 503) (SEQ. ID NO: 513)  
 5'- AGC TGA GAT GGA GGG C -3' (FRAG 504) (SEQ. ID NO: 514)  
 5'- AGC TGA GAT GGA GGG -3' (FRAG 505) (SEQ. ID NO: 515)  
 5'- AGC TGA GAT GGA GG -3' (FRAG 506) (SEQ. ID NO: 516)  
 5'- AGC TGA GAT GGA G -3' (FRAG 507) (SEQ. ID NO: 517)
- 30 5'- AGC TGA GAT GGA -3' (FRAG 508) (SEQ. ID NO: 518)  
 5'- AGC TGA GAT GG -3' (FRAG 509) (SEQ. ID NO: 519)  
 5'- AGC TGA GAT G -3' (FRAG 510) (SEQ. ID NO: 520)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 511) (SEQ. ID NO: 521)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 512) (SEQ. ID NO: 522)
- 35 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 513) (SEQ. ID NO: 523)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 514) (SEQ. ID NO: 524)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT -3' (FRAG 515) (SEQ. ID NO: 525)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 516) (SEQ. ID NO: 526)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 517) (SEQ. ID NO: 527)
- 40 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 518) (SEQ. ID NO: 528)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 519) (SEQ. ID NO: 529)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 520) (SEQ. ID NO: 530)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 521) (SEQ. ID NO: 531)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 522) (SEQ. ID NO: 532)
- 45 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 523) (SEQ. ID NO: 533)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 524) (SEQ. ID NO: 534)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 525) (SEQ. ID NO: 535)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 526) (SEQ. ID NO: 536)  
 5'- GC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 527) (SEQ. ID NO: 537)
- 50 5'- GC TGA GAT GGA GGG CGG CAT G -3' (FRAG 528) (SEQ. ID NO: 538)  
 5'- GC TGA GAT GGA GGG CGG CAT -3' (FRAG 529) (SEQ. ID NO: 539)  
 5'- GC TGA GAT GGA GGG CGG CA-3' (FRAG 530) (SEQ. ID NO: 540)  
 5'- GC TGA GAT GGA GGG CGG C-3' (FRAG 531) (SEQ. ID NO: 541)  
 5'- GC TGA GAT GGA GGG CGG -3' (FRAG 532) (SEQ. ID NO: 542)
- 55 5'- GC TGA GAT GGA GGG CG -3' (FRAG 533) (SEQ. ID NO: 543)  
 5'- GC TGA GAT GGA GGG C -3' (FRAG 534) (SEQ. ID NO: 544)  
 5'- GC TGA GAT GGA GGG -3' (FRAG 535) (SEQ. ID NO: 545)  
 5'- GC TGA GAT GGA GG -3' (FRAG 536) (SEQ. ID NO: 546)  
 5'- GC TGA GAT GGA G -3' (FRAG 537) (SEQ. ID NO: 547)
- 60 5'- GC TGA GAT GGA -3' (FRAG 538) (SEQ. ID NO: 548)  
 5'- GC TGA GAT GG -3' (FRAG 539) (SEQ. ID NO: 549)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 540) (SEQ. ID NO: 550)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 541) (SEQ. ID NO: 551)

5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 542) (SEQ. ID NO: 552)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 543) (SEQ. ID NO: 553)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 544) (SEQ. ID NO: 554)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 545) (SEQ. ID NO: 555)  
 5 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 546) (SEQ. ID NO: 556)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 547) (SEQ. ID NO: 557)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 548) (SEQ. ID NO: 558)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 549) (SEQ. ID NO: 559)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 550) (SEQ. ID NO: 560)  
 10 5'- C TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 551) (SEQ. ID NO: 561)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 552) (SEQ. ID NO: 562)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 553) (SEQ. ID NO: 563)  
 5'- C TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 554) (SEQ. ID NO: 564)  
 5'- C TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 555) (SEQ. ID NO: 565)  
 15 5'- C TGA GAT GGA GGG CGG CAT GG -3' (FRAG 556) (SEQ. ID NO: 566)  
 5'- C TGA GAT GGA GGG CGG CAT G -3' (FRAG 557) (SEQ. ID NO: 567)  
 5'- C TGA GAT GGA GGG CGG CAT -3' (FRAG 558) (SEQ. ID NO: 568)  
 5'- C TGA GAT GGA GGG CGG CA-3' (FRAG 559) (SEQ. ID NO: 569)  
 5'- C TGA GAT GGA GGG CGG C-3' (FRAG 560) (SEQ. ID NO: 570)  
 20 5'- C TGA GAT GGA GGG CGG -3' (FRAG 561) (SEQ. ID NO: 571)  
 5'- C TGA GAT GGA GGG CG -3' (FRAG 562) (SEQ. ID NO: 572)  
 5'- C TGA GAT GGA GGG C -3' (FRAG 563) (SEQ. ID NO: 573)  
 5'- C TGA GAT GGA GGG -3' (FRAG 564) (SEQ. ID NO: 574)  
 5'- C TGA GAT GGA GG -3' (FRAG 565) (SEQ. ID NO: 575)  
 25 5'- C TGA GAT GGA G -3' (FRAG 566) (SEQ. ID NO: 576)  
 5'- C TGA GAT GGA -3' (FRAG 567) (SEQ. ID NO: 577)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 568) (SEQ. ID NO: 578)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 569) (SEQ. ID NO: 579)  
 30 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 570) (SEQ. ID NO: 580)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 571) (SEQ. ID NO: 581)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 572) (SEQ. ID NO: 582)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 573) (SEQ. ID NO: 583)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 574) (SEQ. ID NO: 584)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 575) (SEQ. ID NO: 585)  
 35 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 576) (SEQ. ID NO: 586)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 577) (SEQ. ID NO: 587)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 578) (SEQ. ID NO: 588)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 579) (SEQ. ID NO: 589)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 580) (SEQ. ID NO: 590)  
 40 5'- TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 581) (SEQ. ID NO: 591)  
 5'- TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 582) (SEQ. ID NO: 592)  
 5'- TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 583) (SEQ. ID NO: 593)  
 5'- TGA GAT GGA GGG CGG CAT GG -3' (FRAG 584) (SEQ. ID NO: 594)  
 5'- TGA GAT GGA GGG CGG CAT G -3' (FRAG 585) (SEQ. ID NO: 595)  
 45 5'- TGA GAT GGA GGG CGG CAT -3' (FRAG 586) (SEQ. ID NO: 596)  
 5'- TGA GAT GGA GGG CGG CA-3' (FRAG 587) (SEQ. ID NO: 597)  
 5'- TGA GAT GGA GGG CGG C-3' (FRAG 588) (SEQ. ID NO: 598)  
 5'- TGA GAT GGA GGG CGG -3' (FRAG 589) (SEQ. ID NO: 599)  
 5'- TGA GAT GGA GGG CGG CG -3' (FRAG 590) (SEQ. ID NO: 600)  
 50 5'- TGA GAT GGA GGG C -3' (FRAG 591) (SEQ. ID NO: 601)  
 5'- TGA GAT GGA GGG -3' (FRAG 592) (SEQ. ID NO: 602)  
 5'- TGA GAT GGA GG -3' (FRAG 593) (SEQ. ID NO: 603)  
 5'- TGA GAT GGA G -3' (FRAG 594) (SEQ. ID NO: 604)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 595) (SEQ. ID NO: 605)  
 55 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 596) (SEQ. ID NO: 606)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 597) (SEQ. ID NO: 607)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 598) (SEQ. ID NO: 608)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 599) (SEQ. ID NO: 609)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 600) (SEQ. ID NO: 610)  
 60 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 601) (SEQ. ID NO: 611)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 602) (SEQ. ID NO: 612)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 603) (SEQ. ID NO: 613)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 604) (SEQ. ID NO: 614)

- 5'- GA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 605) (SEQ. ID NO: 615)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 606) (SEQ. ID NO: 616)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 607) (SEQ. ID NO: 617)  
 5'- GA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 608) (SEQ. ID NO: 618)
- 5 5'- GA GAT GGA GGG CGG CAT GGC G-3' (FRAG 609) (SEQ. ID NO: 619)  
 5'- GA GAT GGA GGG CGG CAT GGC -3' (FRAG 610) (SEQ. ID NO: 620)  
 5'- GA GAT GGA GGG CGG CAT GG -3' (FRAG 611) (SEQ. ID NO: 621)  
 5'- GA GAT GGA GGG CGG CAT G -3' (FRAG 612) (SEQ. ID NO: 622)  
 5'- GA GAT GGA GGG CGG CAT -3' (FRAG 613) (SEQ. ID NO: 623)
- 10 5'- GA GAT GGA GGG CGG CA-3' (FRAG 614) (SEQ. ID NO: 624)  
 5'- GA GAT GGA GGG CGG C-3' (FRAG 615) (SEQ. ID NO: 625)  
 5'- GA GAT GGA GGG CGG -3' (FRAG 616) (SEQ. ID NO: 626)  
 5'- GA GAT GGA GGG CG -3' (FRAG 617) (SEQ. ID NO: 627)  
 5'- GA GAT GGA GGG C -3' (FRAG 618) (SEQ. ID NO: 628)
- 15 5'- GA GAT GGA GGG -3' (FRAG 619) (SEQ. ID NO: 629)  
 5'- GA GAT GGA GG -3' (FRAG 620) (SEQ. ID NO: 630)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 621) (SEQ. ID NO: 631)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 622) (SEQ. ID NO: 632)
- 20 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 623) (SEQ. ID NO: 633)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 624) (SEQ. ID NO: 634)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 625) (SEQ. ID NO: 635)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 626) (SEQ. ID NO: 636)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 627) (SEQ. ID NO: 637)
- 25 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 628) (SEQ. ID NO: 638)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 629) (SEQ. ID NO: 639)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 630) (SEQ. ID NO: 640)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 631) (SEQ. ID NO: 641)  
 5'- A GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 632) (SEQ. ID NO: 642)
- 30 5'- A GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 633) (SEQ. ID NO: 643)  
 5'- A GAT GGA GGG CGG CAT GGC GG-3' (FRAG 634) (SEQ. ID NO: 644)  
 5'- A GAT GGA GGG CGG CAT GGC G-3' (FRAG 635) (SEQ. ID NO: 645)  
 5'- A GAT GGA GGG CGG CAT GGC -3' (FRAG 636) (SEQ. ID NO: 646)  
 5'- A GAT GGA GGG CGG CAT GG -3' (FRAG 637) (SEQ. ID NO: 647)
- 35 5'- A GAT GGA GGG CGG CAT G -3' (FRAG 638) (SEQ. ID NO: 648)  
 5'- A GAT GGA GGG CGG CAT -3' (FRAG 639) (SEQ. ID NO: 649)  
 5'- A GAT GGA GGG CGG CA-3' (FRAG 640) (SEQ. ID NO: 650)  
 5'- A GAT GGA GGG CGG C-3' (FRAG 641) (SEQ. ID NO: 651)  
 5'- A GAT GGA GGG CGG -3' (FRAG 642) (SEQ. ID NO: 652)
- 40 5'- A GAT GGA GGG CG -3' (FRAG 643) (SEQ. ID NO: 653)  
 5'- A GAT GGA GGG C -3' (FRAG 644) (SEQ. ID NO: 654)  
 5'- A GAT GGA GGG -3' (FRAG 645) (SEQ. ID NO: 655)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 646) (SEQ. ID NO: 656)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 647) (SEQ. ID NO: 657)
- 45 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 648) (SEQ. ID NO: 658)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 649) (SEQ. ID NO: 659)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 650) (SEQ. ID NO: 660)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 651) (SEQ. ID NO: 661)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 652) (SEQ. ID NO: 662)
- 50 5'- GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 653) (SEQ. ID NO: 663)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 654) (SEQ. ID NO: 664)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 655) (SEQ. ID NO: 665)  
 5'- GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 656) (SEQ. ID NO: 666)  
 5'- GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 657) (SEQ. ID NO: 667)
- 55 5'- GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 658) (SEQ. ID NO: 668)  
 5'- GAT GGA GGG CGG CAT GGC GG-3' (FRAG 659) (SEQ. ID NO: 669)  
 5'- GAT GGA GGG CGG CAT GGC G-3' (FRAG 660) (SEQ. ID NO: 670)  
 5'- GAT GGA GGG CGG CAT GGC -3' (FRAG 661) (SEQ. ID NO: 671)  
 5'- GAT GGA GGG CGG CAT GG -3' (FRAG 662) (SEQ. ID NO: 672)
- 60 5'- GAT GGA GGG CGG CAT G -3' (FRAG 663) (SEQ. ID NO: 673)  
 5'- GAT GGA GGG CGG CAT -3' (FRAG 664) (SEQ. ID NO: 674)  
 5'- GAT GGA GGG CGG CA-3' (FRAG 665) (SEQ. ID NO: 675)  
 5'- GAT GGA GGG CGG C-3' (FRAG 666) (SEQ. ID NO: 676)  
 5'- GAT GGA GGG CGG -3' (FRAG 667) (SEQ. ID NO: 677)

- 5'- GAT GGA GGG CG -3' (FRAG 668) (SEQ. ID NO: 678)  
 5'- GAT GGA GGG C -3' (FRAG 669) (SEQ. ID NO: 679)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 670) (SEQ. ID NO: 680)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 671) (SEQ. ID NO: 681)  
 5 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 672) (SEQ. ID NO: 682)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 673) (SEQ. ID NO: 683)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 674) (SEQ. ID NO: 684)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 675) (SEQ. ID NO: 685)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 676) (SEQ. ID NO: 686)  
 10 5'- AT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 677) (SEQ. ID NO: 687)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 678) (SEQ. ID NO: 688)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 679) (SEQ. ID NO: 689)  
 5'- AT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 680) (SEQ. ID NO: 690)  
 5'- AT GGA GGG CGG CAT GGC GGG C-3' (FRAG 681) (SEQ. ID NO: 691)  
 15 5'- AT GGA GGG CGG CAT GGC GGG -3' (FRAG 682) (SEQ. ID NO: 692)  
 5'- AT GGA GGG CGG CAT GGC GG-3' (FRAG 683) (SEQ. ID NO: 693)  
 5'- AT GGA GGG CGG CAT GGC G-3' (FRAG 684) (SEQ. ID NO: 694)  
 5'- AT GGA GGG CGG CAT GGC -3' (FRAG 685) (SEQ. ID NO: 695)  
 5'- AT GGA GGG CGG CAT GG -3' (FRAG 686) (SEQ. ID NO: 696)  
 20 5'- AT GGA GGG CGG CAT G -3' (FRAG 687) (SEQ. ID NO: 697)  
 5'- AT GGA GGG CGG CAT -3' (FRAG 688) (SEQ. ID NO: 698)  
 5'- AT GGA GGG CGG CA-3' (FRAG 689) (SEQ. ID NO: 699)  
 5'- AT GGA GGG CGG C-3' (FRAG 690) (SEQ. ID NO: 700)  
 5'- AT GGA GGG CGG -3' (FRAG 691) (SEQ. ID NO: 701)  
 25 5'- AT GGA GGG CG -3' (FRAG 692) (SEQ. ID NO: 702)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 693) (SEQ. ID NO: 703)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 694) (SEQ. ID NO: 704)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 695) (SEQ. ID NO: 705)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 696) (SEQ. ID NO: 706)  
 30 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 697) (SEQ. ID NO: 707)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 698) (SEQ. ID NO: 708)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 699) (SEQ. ID NO: 709)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 700) (SEQ. ID NO: 710)  
 5'- T GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 701) (SEQ. ID NO: 711)  
 35 5'- T GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 702) (SEQ. ID NO: 712)  
 5'- T GGA GGG CGG CAT GGC GGG CA-3' (FRAG 703) (SEQ. ID NO: 713)  
 5'- T GGA GGG CGG CAT GGC GGG C-3' (FRAG 704) (SEQ. ID NO: 714)  
 5'- T GGA GGG CGG CAT GGC GGG -3' (FRAG 705) (SEQ. ID NO: 715)  
 5'- T GGA GGG CGG CAT GGC GG-3' (FRAG 706) (SEQ. ID NO: 716)  
 40 5'- T GGA GGG CGG CAT GGC G-3' (FRAG 707) (SEQ. ID NO: 717)  
 5'- T GGA GGG CGG CAT GGC -3' (FRAG 708) (SEQ. ID NO: 718)  
 5'- T GGA GGG CGG CAT GG -3' (FRAG 709) (SEQ. ID NO: 719)  
 5'- T GGA GGG CGG CAT G -3' (FRAG 710) (SEQ. ID NO: 720)  
 5'- T GGA GGG CGG CAT -3' (FRAG 711) (SEQ. ID NO: 721)  
 45 5'- T GGA GGG CGG CA-3' (FRAG 712) (SEQ. ID NO: 722)  
 5'- T GGA GGG CGG C-3' (FRAG 713) (SEQ. ID NO: 723)  
 5'- T GGA GGG CGG -3' (FRAG 714) (SEQ. ID NO: 724)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 715) (SEQ. ID NO: 725)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 716) (SEQ. ID NO: 726)  
 50 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 717) (SEQ. ID NO: 727)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 718) (SEQ. ID NO: 728)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 719) (SEQ. ID NO: 729)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 720) (SEQ. ID NO: 730)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 721) (SEQ. ID NO: 731)  
 55 5'- GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 722) (SEQ. ID NO: 732)  
 5'- GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 723) (SEQ. ID NO: 733)  
 5'- GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 724) (SEQ. ID NO: 734)  
 5'- GGA GGG CGG CAT GGC GGG CA-3' (FRAG 725) (SEQ. ID NO: 735)  
 5'- GGA GGG CGG CAT GGC GGG C-3' (FRAG 726) (SEQ. ID NO: 736)  
 60 5'- GGA GGG CGG CAT GGC GGG -3' (FRAG 727) (SEQ. ID NO: 737)  
 5'- GGA GGG CGG CAT GGC GG-3' (FRAG 728) (SEQ. ID NO: 738)  
 5'- GGA GGG CGG CAT GGC G-3' (FRAG 729) (SEQ. ID NO: 739)  
 5'- GGA GGG CGG CAT GGC -3' (FRAG 730) (SEQ. ID NO: 740)

- 5'- GGA GGG CGG CAT GG -3' (FRAG 731) (SEQ. ID NO: 741)  
 5'- GGA GGG CGG CAT G -3' (FRAG 732) (SEQ. ID NO: 742)  
 5'- GGA GGG CGG CAT -3' (FRAG 733) (SEQ. ID NO: 743)  
 5'- GGA GGG CGG CA-3' (FRAG 734) (SEQ. ID NO: 744)  
 5 5'- GGA GGG CGG C-3' (FRAG 735) (SEQ. ID NO: 745)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 736) (SEQ. ID NO: 746)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 737) (SEQ. ID NO: 747)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 738) (SEQ. ID NO: 748)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 739) (SEQ. ID NO: 749)  
 10 5'- GA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 740) (SEQ. ID NO: 750)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 741) (SEQ. ID NO: 751)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 742) (SEQ. ID NO: 752)  
 5'- GA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 743) (SEQ. ID NO: 753)  
 5'- GA GGG CGG CAT GGC GGG CAC A-3' (FRAG 744) (SEQ. ID NO: 754)  
 15 5'- GA GGG CGG CAT GGC GGG CAC-3' (FRAG 745) (SEQ. ID NO: 755)  
 5'- GA GGG CGG CAT GGC GGG CA-3' (FRAG 746) (SEQ. ID NO: 756)  
 5'- GA GGG CGG CAT GGC GGG C-3' (FRAG 747) (SEQ. ID NO: 757)  
 5'- GA GGG CGG CAT GGC GGG -3' (FRAG 748) (SEQ. ID NO: 758)  
 5'- GA GGG CGG CAT GGC GG-3' (FRAG 749) (SEQ. ID NO: 759)  
 20 5'- GA GGG CGG CAT GGC G-3' (FRAG 750) (SEQ. ID NO: 760)  
 5'- GA GGG CGG CAT GGC -3' (FRAG 751) (SEQ. ID NO: 761)  
 5'- GA GGG CGG CAT GG -3' (FRAG 752) (SEQ. ID NO: 762)  
 5'- GA GGG CGG CAT G -3' (FRAG 753) (SEQ. ID NO: 763)  
 5'- GA GGG CGG CAT -3' (FRAG 754) (SEQ. ID NO: 764)  
 25 5'- GA GGG CGG CA-3' (FRAG 755) (SEQ. ID NO: 765)  
 5'- A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 756) (SEQ. ID NO: 766)  
 5'- A GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 757) (SEQ. ID NO: 767)  
 5'- A GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 758) (SEQ. ID NO: 768)  
 5'- A GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 759) (SEQ. ID NO: 769)  
 30 5'- A GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 760) (SEQ. ID NO: 770)  
 5'- A GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 761) (SEQ. ID NO: 771)  
 5'- A GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 762) (SEQ. ID NO: 772)  
 5'- A GGG CGG CAT GGC GGG CAC AG-3' (FRAG 763) (SEQ. ID NO: 773)  
 5'- A GGG CGG CAT GGC GGG CAC A-3' (FRAG 764) (SEQ. ID NO: 774)  
 35 5'- A GGG CGG CAT GGC GGG CAC-3' (FRAG 765) (SEQ. ID NO: 775)  
 5'- A GGG CGG CAT GGC GGG CA-3' (FRAG 766) (SEQ. ID NO: 776)  
 5'- A GGG CGG CAT GGC GGG C-3' (FRAG 767) (SEQ. ID NO: 777)  
 5'- A GGG CGG CAT GGC GGG -3' (FRAG 768) (SEQ. ID NO: 778)  
 5'- A GGG CGG CAT GGC GG-3' (FRAG 769) (SEQ. ID NO: 779)  
 40 5'- A GGG CGG CAT GGC G-3' (FRAG 770) (SEQ. ID NO: 780)  
 5'- A GGG CGG CAT GGC -3' (FRAG 771) (SEQ. ID NO: 781)  
 5'- A GGG CGG CAT GG -3' (FRAG 772) (SEQ. ID NO: 782)  
 5'- A GGG CGG CAT G -3' (FRAG 773) (SEQ. ID NO: 783)  
 5'- A GGG CGG CAT -3' (FRAG 774) (SEQ. ID NO: 784)  
 45 5'- GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 775) (SEQ. ID NO: 785)  
 5'- GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 776) (SEQ. ID NO: 786)  
 5'- GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 777) (SEQ. ID NO: 787)  
 5'- GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 778) (SEQ. ID NO: 788)  
 5'- GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 779) (SEQ. ID NO: 789)  
 50 5'- GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 780) (SEQ. ID NO: 790)  
 5'- GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 781) (SEQ. ID NO: 791)  
 5'- GGG CGG CAT GGC GGG CAC AG-3' (FRAG 782) (SEQ. ID NO: 792)  
 5'- GGG CGG CAT GGC GGG CAC A-3' (FRAG 783) (SEQ. ID NO: 793)  
 5'- GGG CGG CAT GGC GGG CAC-3' (FRAG 784) (SEQ. ID NO: 794)  
 55 5'- GGG CGG CAT GGC GGG CA-3' (FRAG 785) (SEQ. ID NO: 795)  
 5'- GGG CGG CAT GGC GGG C-3' (FRAG 786) (SEQ. ID NO: 796)  
 5'- GGG CGG CAT GGC GGG -3' (FRAG 787) (SEQ. ID NO: 797)  
 5'- GGG CGG CAT GGC GG-3' (FRAG 788) (SEQ. ID NO: 798)  
 5'- GGG CGG CAT GGC G-3' (FRAG 789) (SEQ. ID NO: 799)  
 60 5'- GGG CGG CAT GGC -3' (FRAG 790) (SEQ. ID NO: 800)  
 5'- GGG CGG CAT GG -3' (FRAG 791) (SEQ. ID NO: 801)  
 5'- GGG CGG CAT G -3' (FRAG 792) (SEQ. ID NO: 802)  
 5'- GG CGG CAT GGC GGG CAC AG G CTG GGC-3' (FRAG 793) (SEQ. ID NO: 803)

5' GG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 794) (SEQ. ID NO: 804)  
 5' GG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 795) (SEQ. ID NO: 805)  
 5' GG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 796) (SEQ. ID NO: 806)  
 5' GG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 797) (SEQ. ID NO: 807)  
 5 5' GG CGG CAT GGC GGG CAC AGG C-3' (FRAG 798) (SEQ. ID NO: 808)  
 5' GG CGG CAT GGC GGG CAC AGG -3' (FRAG 799) (SEQ. ID NO: 809)  
 5' GG CGG CAT GGC GGG CAC AG-3' (FRAG 800) (SEQ. ID NO: 810)  
 5' GG CGG CAT GGC GGG CAC A-3' (FRAG 801) (SEQ. ID NO: 811)  
 5' GG CGG CAT GGC GGG CAC-3' (FRAG 802) (SEQ. ID NO: 812)  
 10 5' GG CGG CAT GGC GGG CA-3' (FRAG 803) (SEQ. ID NO: 813)  
 5' GG CGG CAT GGC GGG C-3' (FRAG 804) (SEQ. ID NO: 814)  
 5' GG CGG CAT GGC GGG -3' (FRAG 805) (SEQ. ID NO: 815)  
 5' GG CGG CAT GGC GG-3' (FRAG 806) (SEQ. ID NO: 816)  
 5' GG CGG CAT GGC G-3' (FRAG 807) (SEQ. ID NO: 817)  
 15 5' GG CGG CAT GGC -3' (FRAG 808) (SEQ. ID NO: 818)  
 5' GG CGG CAT GG -3' (FRAG 809) (SEQ. ID NO: 819)  
 5' G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 810) (SEQ. ID NO: 820)  
 5' G CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 811) (SEQ. ID NO: 821)  
 5' G CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 812) (SEQ. ID NO: 822)  
 20 5' G CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 813) (SEQ. ID NO: 823)  
 5' G CGG CAT GGC GGG CAC AGG CT-3' (FRAG 814) (SEQ. ID NO: 824)  
 5' G CGG CAT GGC GGG CAC AGG C-3' (FRAG 815) (SEQ. ID NO: 825)  
 5' G CGG CAT GGC GGG CAC AGG -3' (FRAG 816) (SEQ. ID NO: 826)  
 5' G CGG CAT GGC GGG CAC AG-3' (FRAG 817) (SEQ. ID NO: 827)  
 25 5' G CGG CAT GGC GGG CAC A-3' (FRAG 818) (SEQ. ID NO: 828)  
 5' G CGG CAT GGC GGG CAC-3' (FRAG 819) (SEQ. ID NO: 829)  
 5' G CGG CAT GGC GGG CA-3' (FRAG 820) (SEQ. ID NO: 830)  
 5' G CGG CAT GGC GGG C-3' (FRAG 821) (SEQ. ID NO: 831)  
 5' G CGG CAT GGC GGG -3' (FRAG 822) (SEQ. ID NO: 832)  
 30 5' G CGG CAT GGC GG-3' (FRAG 823) (SEQ. ID NO: 833)  
 5' G CGG CAT GGC G-3' (FRAG 824) (SEQ. ID NO: 834)  
 5' G CGG CAT GGC -3' (FRAG 825) (SEQ. ID NO: 835)  
 5' CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 826) (SEQ. ID NO: 836)  
 5' CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 827) (SEQ. ID NO: 837)  
 35 5' CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 828) (SEQ. ID NO: 838)  
 5' CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 829) (SEQ. ID NO: 839)  
 5' CGG CAT GGC GGG CAC AGG CT-3' (FRAG 830) (SEQ. ID NO: 840)  
 5' CGG CAT GGC GGG CAC AGG C-3' (FRAG 831) (SEQ. ID NO: 841)  
 5' CGG CAT GGC GGG CAC AGG -3' (FRAG 832) (SEQ. ID NO: 842)  
 40 5' CGG CAT GGC GGG CAC AG-3' (FRAG 833) (SEQ. ID NO: 843)  
 5' CGG CAT GGC GGG CAC A-3' (FRAG 834) (SEQ. ID NO: 844)  
 5' CGG CAT GGC GGG CAC-3' (FRAG 835) (SEQ. ID NO: 845)  
 5' CGG CAT GGC GGG CA-3' (FRAG 836) (SEQ. ID NO: 846)  
 5' CGG CAT GGC GGG C-3' (FRAG 837) (SEQ. ID NO: 847)  
 45 5' CGG CAT GGC GGG -3' (FRAG 838) (SEQ. ID NO: 848)  
 5' CGG CAT GGC GG-3' (FRAG 839) (SEQ. ID NO: 849)  
 5' CGG CAT GGC G-3' (FRAG 840) (SEQ. ID NO: 850)  
 5' GG CAT GGC GGG CAC AGG C TG GGC-3' (FRAG 841) (SEQ. ID NO: 851)  
 5' GG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 842) (SEQ. ID NO: 852)  
 50 5' GG CAT GGC GGG CAC AGG CTG G-3' (FRAG 843) (SEQ. ID NO: 853)  
 5' GG CAT GGC GGG CAC AGG CTG -3' (FRAG 844) (SEQ. ID NO: 854)  
 5' GG CAT GGC GGG CAC AGG CT-3' (FRAG 845) (SEQ. ID NO: 855)  
 5' GG CAT GGC GGG CAC AGG C-3' (FRAG 846) (SEQ. ID NO: 856)  
 5' GG CAT GGC GGG CAC AGG -3' (FRAG 847) (SEQ. ID NO: 857)  
 55 5' GG CAT GGC GGG CAC AG-3' (FRAG 848) (SEQ. ID NO: 858)  
 5' GG CAT GGC GGG CAC A-3' (FRAG 849) (SEQ. ID NO: 859)  
 5' GG CAT GGC GGG CAC-3' (FRAG 850) (SEQ. ID NO: 860)  
 5' GG CAT GGC GGG CA-3' (FRAG 851) (SEQ. ID NO: 861)  
 5' GG CAT GGC GGG C-3' (FRAG 852) (SEQ. ID NO: 862)  
 60 5' GG CAT GGC GGG -3' (FRAG 853) (SEQ. ID NO: 863)  
 5' GG CAT GGC GG-3' (FRAG 854) (SEQ. ID NO: 864)  
 5' G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 855) (SEQ. ID NO: 865)  
 5' G CAT GGC GGG CAC AGG CTG GG-3' (FRAG 856) (SEQ. ID NO: 866)

5' G CAT GGC GGG CAC AGG CTG G-3' (FRAG 857) (SEQ. ID NO: 867)  
 5' G CAT GGC GGG CAC AGG CTG -3' (FRAG 858) (SEQ. ID NO: 868)  
 5' G CAT GGC GGG CAC AGG CT-3' (FRAG 859) (SEQ. ID NO: 869)  
 5' G CAT GGC GGG CAC AGG C-3' (FRAG 860) (SEQ. ID NO: 870)  
 5 5' G CAT GGC GGG CAC AGG -3' (FRAG 861) (SEQ. ID NO: 871)  
 5' G CAT GGC GGG CAC AG-3' (FRAG 862) (SEQ. ID NO: 872)  
 5' G CAT GGC GGG CAC A-3' (FRAG 863) (SEQ. ID NO: 873)  
 5' G CAT GGC GGG CAC-3' (FRAG 864) (SEQ. ID NO: 874)  
 5' G CAT GGC GGG CA-3' (FRAG 865) (SEQ. ID NO: 875)  
 10 5' G CAT GGC GGG C-3' (FRAG 866) (SEQ. ID NO: 876)  
 5' G CAT GGC GGG -3' (FRAG 867) (SEQ. ID NO: 877)  
 5' CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 868) (SEQ. ID NO: 878)  
 5' CAT GGC GGG CAC AGG CTG GG-3' (FRAG 869) (SEQ. ID NO: 879)  
 5' CAT GGC GGG CAC AGG CTG G-3' (FRAG 870) (SEQ. ID NO: 880)  
 15 5' CAT GGC GGG CAC AGG CTG -3' (FRAG 871) (SEQ. ID NO: 881)  
 5' CAT GGC GGG CAC AGG CT-3' (FRAG 872) (SEQ. ID NO: 882)  
 5' CAT GGC GGG CAC AGG C-3' (FRAG 873) (SEQ. ID NO: 883)  
 5' CAT GGC GGG CAC AGG -3' (FRAG 874) (SEQ. ID NO: 884)  
 5' CAT GGC GGG CAC AG-3' (FRAG 875) (SEQ. ID NO: 885)  
 20 5' CAT GGC GGG CAC A-3' (FRAG 876) (SEQ. ID NO: 886)  
 5' CAT GGC GGG CAC-3' (FRAG 877) (SEQ. ID NO: 887)  
 5' CAT GGC GGG CA-3' (FRAG 878) (SEQ. ID NO: 888)  
 5' CAT GGC GGG C-3' (FRAG 879) (SEQ. ID NO: 889)  
 5' AT GGC GGG CAC AGG CTG GGC-3' (FRAG 880) (SEQ. ID NO: 890)  
 25 5' AT GGC GGG CAC AGG CTG GG-3' (FRAG 881) (SEQ. ID NO: 891)  
 5' AT GGC GGG CAC AGG CTG G-3' (FRAG 882) (SEQ. ID NO: 892)  
 5' AT GGC GGG CAC AGG CTG -3' (FRAG 883) (SEQ. ID NO: 893)  
 5' AT GGC GGG CAC AGG CT-3' (FRAG 884) (SEQ. ID NO: 894)  
 30 5' AT GGC GGG CAC AGG C-3' (FRAG 885) (SEQ. ID NO: 895)  
 5' AT GGC GGG CAC AGG -3' (FRAG 886) (SEQ. ID NO: 896)  
 5' AT GGC GGG CAC AG-3' (FRAG 887) (SEQ. ID NO: 897)  
 5' AT GGC GGG CAC A-3' (FRAG 888) (SEQ. ID NO: 898)  
 5' AT GGC GGG CAC-3' (FRAG 889) (SEQ. ID NO: 899)  
 5' AT GGC GGG CA-3' (FRAG 890) (SEQ. ID NO: 900)  
 35 5' T GGC GGG CAC AGG CTG GGC-3' (FRAG 891) (SEQ. ID NO: 901)  
 5' T GGC GGG CAC AGG CTG GG-3' (FRAG 892) (SEQ. ID NO: 902)  
 5' T GGC GGG CAC AGG CTG G-3' (FRAG 893) (SEQ. ID NO: 903)  
 5' T GGC GGG CAC AGG CTG -3' (FRAG 894) (SEQ. ID NO: 904)  
 5' T GGC GGG CAC AGG CT-3' (FRAG 895) (SEQ. ID NO: 905)  
 40 5' T GGC GGG CAC AGG C-3' (FRAG 896) (SEQ. ID NO: 906)  
 5' T GGC GGG CAC AGG -3' (FRAG 897) (SEQ. ID NO: 907)  
 5' T GGC GGG CAC AG-3' (FRAG 898) (SEQ. ID NO: 908)  
 5' T GGC GGG CAC A-3' (FRAG 899) (SEQ. ID NO: 909)  
 5' T GGC GGG CAC-3' (FRAG 900) (SEQ. ID NO: 910)  
 45 5' GGC GGG CAC AGG CTG GGC-3' (FRAG 901) (SEQ. ID NO: 911)  
 5' GGC GGG CAC AGG CTG GG-3' (FRAG 902) (SEQ. ID NO: 912)  
 5' GGC GGG CAC AGG CTG G-3' (FRAG 903) (SEQ. ID NO: 913)  
 5' GGC GGG CAC AGG CTG -3' (FRAG 904) (SEQ. ID NO: 914)  
 5' GGC GGG CAC AGG CT-3' (FRAG 905) (SEQ. ID NO: 915)  
 50 5' GGC GGG CAC AGG C-3' (FRAG 906) (SEQ. ID NO: 916)  
 5' GGC GGG CAC AGG -3' (FRAG 907) (SEQ. ID NO: 917)  
 5' GGC GGG CAC AG-3' (FRAG 908) (SEQ. ID NO: 918)  
 5' GGC GGG CAC A-3' (FRAG 909) (SEQ. ID NO: 919)  
 55 5' GC GGG CAC AGG CTG GGC-3' (FRAG 910) (SEQ. ID NO: 920)  
 5' GC GGG CAC AGG CTG GG-3' (FRAG 911) (SEQ. ID NO: 921)  
 5' GC GGG CAC AGG CTG G-3' (FRAG 912) (SEQ. ID NO: 922)  
 5' GC GGG CAC AGG CTG -3' (FRAG 913) (SEQ. ID NO: 923)  
 5' GC GGG CAC AGG CT-3' (FRAG 914) (SEQ. ID NO: 924)  
 5' GC GGG CAC AGG C-3' (FRAG 915) (SEQ. ID NO: 925)  
 60 5' GC GGG CAC AGG -3' (FRAG 916) (SEQ. ID NO: 926)  
 5' GC GGG CAC AG-3' (FRAG 917) (SEQ. ID NO: 927)  
 5' C GGG CAC AGG CTG GGC-3' (FRAG 918) (SEQ. ID NO: 928)

5'- C GGG CAC AGG CTG GG-3' (FRAG 919) (SEQ. ID NO: 929)  
 5'- C GGG CAC AGG CTG G-3' (FRAG 920) (SEQ. ID NO: 930)  
 5'- C GGG CAC AGG CTG -3' (FRAG 921) (SEQ. ID NO: 931)  
 5'- C GGG CAC AGG CT-3' (FRAG 922) (SEQ. ID NO: 932)  
 5 5'- C GGG CAC AGG C-3' (FRAG 923) (SEQ. ID NO: 933)  
 5'- C GGG CAC AGG -3' (FRAG 924) (SEQ. ID NO: 934)  
 5'- GGG CAC AGG CTG GGC-3' (FRAG 925) (SEQ. ID NO: 935)  
 5'- GGG CAC AGG CTG GG-3' (FRAG 926) (SEQ. ID NO: 936)  
 5'- GGG CAC AGG CTG G-3' (FRAG 927) (SEQ. ID NO: 937)  
 10 5'- GGG CAC AGG CTG -3' (FRAG 928) (SEQ. ID NO: 938)  
 5'- GGG CAC AGG CT-3' (FRAG 929) (SEQ. ID NO: 939)  
 5'- GGG CAC AGG C-3' (FRAG 930) (SEQ. ID NO: 940)  
 5'- GG CAC AGG CTG GGC-3' (FRAG 931) (SEQ. ID NO: 941)  
 5'- GG CAC AGG CTG GG-3' (FRAG 932) (SEQ. ID NO: 942)  
 15 5'- GG CAC AGG CTG G-3' (FRAG 933) (SEQ. ID NO: 943)  
 5'- GG CAC AGG CTG -3' (FRAG 934) (SEQ. ID NO: 944)  
 5'- GG CAC AGG CT-3' (FRAG 935) (SEQ. ID NO: 945)  
 5'- G CAC AGG CTG GGC-3' (FRAG 936) (SEQ. ID NO: 946)  
 5'- G CAC AGG CTG GG-3' (FRAG 937) (SEQ. ID NO: 947)  
 20 5'- G CAC AGG CTG G-3' (FRAG 938) (SEQ. ID NO: 948)  
 5'- G CAC AGG CTG -3' (FRAG 939) (SEQ. ID NO: 949)  
 5'- CAC AGG CTG GGC-3' (FRAG 940) (SEQ. ID NO: 950)  
 5'- CAC AGG CTG GG-3' (FRAG 941) (SEQ. ID NO: 951)  
 5'- CAC AGG CTG G-3' (FRAG 942) (SEQ. ID NO: 952)  
 25 5'- AC AGG CTG GGC-3' (FRAG 943) (SEQ. ID NO: 953)  
 5'- AC AGG CTG GG-3' (FRAG 944) (SEQ. ID NO: 954)  
 5'- C AGG CTG GGC-3' (FRAG 945) (SEQ. ID NO: 955)

In the anti-sense oligonucleotides of the present invention, exemplified by the preceding sequences, adenine bases may be replaced with an appropriate "spacer" or  
 30 universal base (e.g., 1-[ $\beta$ -D-2'-deoxyribofuranosyl]-5-nitroindole], or with an adenosine agonist or antagonist that does not stimulate adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> or A<sub>3</sub> receptors or the bradykinin B<sub>2</sub> receptor.

Examples of anti-sense oligo sequences targeted to the adenosine A<sub>2b</sub> receptors are as follows.

35 35' GGC CGG GCC AGC TGG GCC CCG GGC GCC C (SEQ ID NO: 8)  
 GGC CGG GCC AGC TGG GCC CCG G (FRAG 1)  
 CTC CAG CAG CAT GGC CGG GCC (FRAG 2)  
 CGC CGT GCC CAC CGC GGC GC (FRAG 3)  
 GCC CCA CGG CCA CGT CGG CCC C (FRAG 4)

40 Fragments of SEQ. ID NO: 7 and 8 shown above other than the ones exemplified, which are about 7 to 18 nucleotide long are also encompassed and preferred. Particularly preferred are those where the 3' end is preferentially conserved.

Anti-sense oligos specific to the human adenosine A<sub>2a</sub> receptor are exemplified below. For gene sequence, see Salvatore, C. A., et al., Genomics (1997). Fragments of the two  
 45 sequences shown below about 7 to 18 nucleotide long are also encompassed and preferred. Particularly preferred are those where the 3' end is preferentially conserved.

GGA GCC CAT GAT GGG CAT GCC (FRAG 1) CCC ACT GCG ATG TCG GCC GCC GCC (FRAG 2)  
GGC CCT CCC CGC AGC CCT GGG (FRAG 3) CTT CAG CTG TCG TCG GCG CGC C (FRAG 4) (SEQ.  
ID NO: 9)

5 GGA CCG TGC CCG CTC CCC CGG C (FRAG 1) TGC AGT GTG GAC CGT GCC CGC (FRAG 2) GGG  
CGT GGC TGC AGT CGG GGC (FRAG 3) GGC CCA CAC TCC TGG CGG GTG GCC G (FRAG 4) GCC  
GTT GGC CCA CAC TCC TGG CGG G (FRAG 5) (SEQ. ID NO: 10)

Chemical analogs of oligonucleotides, e.g., oligonucleotides in which the phosphodiester bonds have been modified, e.g., to the methylphosphonate, the phosphotriester, the phosphorothioate, the phosphorodithioate, or the phosphoramidate, so 10 as to render the oligonucleotide more stable in vivo, are also an aspect of the present invention. The naturally occurring phosphodiester linkages in oligonucleotides are susceptible to degradation by endogenously occurring cellular nucleases, while many analogous linkages are highly resistant to nuclease degradation. See Milligan et al., *supra*; Cohen, J. S. D., *supra*. Protection from degradation can be achieved by use of a "3'-end cap" strategy by 15 which nuclease-resistant linkages are substituted for phosphodiester linkages at the 3' end of the oligonucleotide. See Tidd, D. M. and Warenius, H. M., *Br. J. Cancer* 60, 343-350 (1989); Shaw, J.P. et al., *Nucleic Acids Res.* 19, 747-750 (1991). Phosphoramidates, phosphorothioates, and methylphosphonate linkages all function adequately in this manner. More extensive modification of the phosphodiester backbone has been shown to impart 20 stability and may allow for enhanced affinity and increased cellular permeation of oligonucleotides. See Milligan, et al., *supra*. Many different chemical strategies have been employed to replace the entire phosphodiester backbone with novel linkages. Id. Backbone analogues include phosphorothioate, methylphosphonate, phosphotriester, thioformacetal, phosphorodithioate, phosphoramidate, formacetal boranophosphate, 3'-thioformacetal, 2'-O- 25 methyl, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methylimino) (MMI) or methyleneoxy(methylimino) (MOMI) linkages. Phosphorothioate and methylphosphonate-modified oligonucleotides are particularly preferred due to their availability through automated oligonucleotide synthesis. Id. Anti-sense oligonucleotides containing 30 modifications to the nucleotide base itself, e.g. a C-5 propyne, or C-5 methyl, or to the sugar, e.g. a carbohydrate modification, are also aspects of the present invention. Where appropriate, the anti-sense nucleotide may be administered in the form of their pharmaceutically acceptable salts.

The present anti-sense oligonucleotides may be of any suitable length, preferably about 7 to 60, more preferably about 10 to 36, and still more preferably about 12 to 21, nucleotide long, depending on the particular target being bound and the mode of delivery thereof. Preferably the anti-sense oligonucleotide is directed to an mRNA region containing

5 a junction between intron and exon. Where the anti-sense oligonucleotide is directed to an intron/exon junction, it may either entirely overlie the junction or may be sufficiently close to the junction to inhibit splicing out of the intervening exon during processing of precursor mRNA to mature mRNA, e.g. with the 3' or 5' terminus of the anti-sense oligonucleotide being positioned within about, for example, 10, 5, 3, or 2 nucleotide of the intron/exon

10 junction. Also preferred are anti-sense oligonucleotides which overlap the initiation codon. When administering the anti-sense oligos of the present invention, their sequence may be drawn from a gene or RNA sequence related in origin to the species to which it is administered. When treating humans, human anti-sense may be used if desired.

The agent of the invention is also provided as a pharmaceutical composition

15 comprising an anti-sense oligonucleotide as given above effective to reduce expression of an adenosine and/or bradykinin receptor gene, particularly the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and/or A<sub>3</sub> and bradykinin B<sub>2</sub> receptors by passing through a cell membrane and selectively binding to mRNA encoding the receptor mRNA in the cell so as to prevent its translation. Such compositions are provided in suitable formulations, accompanied by a carrier, preferably a

20 pharmaceutically or veterinarianily acceptable carrier, e.g. sterile pyrogen-free saline solution. The anti-sense oligonucleotides may be formulated with a hydrophobic carrier capable of passing through a cell membrane (e.g., in a liposome, with the liposomes carried in a pharmaceutically acceptable aqueous carrier). The sequence specific oligonucleotides may also be constructed so as to compose an entity which directly inactivates mRNA, such as a

25 ribozyme. Such oligonucleotides may be administered to a subject in need of the treatment to inhibit the activation of adenosine receptors, such as the adenosine A<sub>1</sub>, A<sub>2b</sub>, A<sub>2b</sub> and/or A<sub>3</sub> and the bradykinin B<sub>2</sub> receptors. Furthermore, the pharmaceutical formulation may also contain chimeric molecules comprising anti-sense oligonucleotides attached to agents which are known to be internalized and/or taken-up by lysing cells. These oligonucleotide

30 conjugates utilize cellular up-take pathways to increase cellular concentrations of oligonucleotides. Examples of macromolecules used in this manner include transferrin, asialoglycoprotein (bound to oligonucleotides via polylysine) and streptavidin.

In the pharmaceutical formulation the anti-sense oligo may be contained within a lipid particle or vesicle, such as a liposome or microcrystal. The particles may be of any suitable structure, such as unilamellar or plurilamellar, so long as the anti-sense oligonucleotide is contained therein. Positively charged lipids, such as N-[1-(2, 3-dioleyloxi) propyl] -N, N,

5 N-trimethylammoniummethylsulfate or "DOTAP", are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known. See, e.g., U.S. Patent Nos. 4,880,635 to Janoff et al.; 4,906,477 to Kurono et al.; 4,911,928 to Wallach; 4,917,951 to Wallach; 4,920,016 to Allen et al.; 4,921,757 to Wheatley et al.; etc.

The composition of this invention may be administered to a subject by any means of delivery which will transport the anti-sense nucleotide composition to the lung. The anti-sense oligos of this invention may be administered to the lungs of a patient by any suitable means, but are preferably administered by generating an aerosol comprised of respirable particles, the respirable particles comprised of the anti-sense compound, which particles the subject inhales. The respirable particles may be liquid or solid. The particles may optionally contain other therapeutic ingredients.

The anti-sense compound of the present invention is generally delivered in particulate form. The particles should include particles of respirable size, preferably particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. In general, particles ranging from about 0.5 to 10 microns in size

20 are respirable. Particles of non-respirable size which are included in the aerosol tend to deposit in the throat and be swallowed, and the quantity of non-respirable particles in the aerosol is preferably minimized. For nasal administration, a particle size in the range of 10-500  $\mu\text{m}$  is preferred to ensure retention in the nasal cavity.

Liquid pharmaceutical compositions of active compound for producing an aerosol can

25 be prepared by combining the anti-sense compound with a suitable vehicle, such as sterile pyrogen free water. Other therapeutic compounds may optionally be included.

Solid particulate compositions containing respirable dry particles of micronized anti-sense compound may be prepared by grinding dry anti-sense compound with a mortar and pestle, and then passing the micronized composition through a 400 mesh screen to break up

30 or separate out large agglomerates. A solid particulate composition comprised of the anti-sense compound may optionally contain a dispersant which serves to facilitate the formation of an aerosol. A suitable dispersant is lactose, which may be blended with the anti-sense

compound in any suitable ratio, e.g. an about 1:1 ratio by weight. Again, other therapeutic compounds may also be included.

The dosage of the anti-sense compound administered will depend upon the disease being treated, the condition of the subject, the particular formulation, the route of administration, the timing of administration to a subject, etc. In general, intracellular concentrations of the oligonucleotide of from 0.05 to 50  $\mu\text{M}$ , or more particularly 0.2 to 5  $\mu\text{M}$ , are desirable, however higher or lower concentrations may also be therapeutic. For administration to a subject such as a human, a dosage of about 0.01, 0.1, or 1 mg/Kg up to 50, 100, or 150 mg/Kg or more, is typically employed. Depending on the solubility of the particular formulation of active compound administered, the daily dose may be divided among one or several unit dose administrations. Administration of the anti-sense compounds may be carried out therapeutically (i.e., as a rescue treatment) or prophylactically.

Aerosols of liquid particles comprising the anti-sense compound may be produced by any suitable means, such as with a nebulizer. See, e.g., US Patent No. 4,501,729. 15 Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier, the active ingredient comprising about 0.01 % to about 40% w/w of the 20 formulation, and higher, preferably up to about 20% w/w. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and surfactants.

25         Aerosols of solid particles comprising the active compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. One illustrative type of solid 30 particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the

powder (e.g., a metered dose thereof effective to carry out the treatments described herein) is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator

5     consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of

10    the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150  $\mu\text{l}$ , to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. Additionally, other

15    propellants having improved environmental properties as compared to fluor- and chlorofluorocarbon compounds may be employed. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents.

The aerosol, whether formed from solid or liquid particles, may be produced by the

20    aerosol generator at a rate of from about 10 to 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament may be administered more rapidly.

The following examples are provided to illustrate the present invention, and should not be construed as limiting thereon.

## 25

### EXAMPLES

In the following examples,  $\mu\text{M}$  means micromolar, mL means milliliters,  $\mu\text{m}$  means micrometers, mm means millimeters, cm means centimeters,  $^{\circ}\text{C}$  means degrees Celsius,  $\mu\text{g}$  means micrograms, mg means milligrams, g means grams, kg means kilograms, M means molar, and h or hr means hours.

30    **Example 1: Design and Synthesis of Anti-sense Oligonucleotides**

The design of anti-sense oligonucleotides against the  $A_1$  and  $A_2$  adenosine receptors may require the solution of the complex secondary structure of the target  $A_1$  receptor mRNA,

the target A<sub>2a</sub> receptor mRNA, the target A<sub>2b</sub> receptor mRNA and the target A<sub>3</sub> receptor mRNA. After generating this structure, anti-sense nucleotide are designed which target regions of mRNA which might be construed to confer functional activity or stability to the mRNA and which optimally may overlap the initiation codon. Other target sites are readily 5 usable. As a demonstration of specificity of the anti-sense effect, other oligonucleotides not totally complementary to the target mRNA, but containing identical nucleotide compositions on a w/w basis, are included as controls in anti-sense experiments.

Adenosine A<sub>1</sub> receptor mRNA secondary structure was analyzed and used as described above to design a phosphorothioate anti-sense oligonucleotide. The anti-sense oligonucleotide 10 which was synthesized was designated HAdAlAS and had the following sequence:

5' -GAT GCA GGG CGG CAT GGC GGG-3' (SEQ ID NO:1)

As a control, a mismatched phosphorothioate anti-sense nucleotide designated HAdAlMM was synthesized with the following sequence:

GTA GGT GGC GGG CAA GGC GGG (SEQ ID NO:2)

15 Each oligonucleotide had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligonucleotide was specific for the human and rabbit adenosine A<sub>1</sub> receptor genes, and that the mismatched control was not a candidate for hybridization with any known gene sequence.

20 Adenosine A<sub>2</sub> receptor mRNA secondary structure was similarly analyzed and used as described above to design two phosphorothioate anti-sense oligonucleotides. The first anti-sense oligonucleotide (HAdA3AS1) synthesized had the following sequence:

5' -GTT GTT GGG CAT CTT GCC-3' (SEQ ID NO:3)

As a control, a mismatched phosphorothioate anti-sense oligonucleotide (HAdA3MM1) was 25 synthesized, having the following sequence:

5' -GTA CTT GCG GAT CTA GGC-3' (SEQ ID NO:4)

A second phosphorothioate anti-sense oligonucleotide (HAdA3AS2) was also designed and synthesized, having the following sequence:

5' -GTG GGC CTA GCT CTC GCC-3' (SEQ ID NO:5)

30 Its control oligonucleotide (HAdA3MM2) had the sequence:

5' -GTC GGG GTA CCT GTC GGC-3' (SEQ ID NO:6)

Phosphorothioate oligonucleotides were synthesized on an Applied Biosystems Model

396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, MD).

**Example 2: In Vitro Effect of Adenosine A<sub>1</sub> Receptor Anti-sense Oligonucleotides**

5       The anti-sense oligonucleotide against the human A<sub>1</sub> receptor (SEQ ID NO:1) described above was tested for efficacy in an in vitro model utilizing lung adenocarcinoma cells HTB-54. HTB-54 lung adenocarcinoma cells were demonstrated to express the A<sub>1</sub> adenosine receptor using standard northern blotting procedures and receptor probes designed and synthesized in the laboratory.

10      HTB-54 human lung adenocarcinoma cells (10<sup>6</sup>/100 mm tissue culture dish) were exposed to 5.0 μM HAdAlAS (SEQ. ID NO:1) or HAdAlMM (SEQ. ID NO:2) for 24 hours, with a fresh change of media and oligonucleotides after 12 hours of incubation. Following 24 hour exposure to the oligonucleotides, cells were harvested and their RNA extracted by standard procedures. A 21-mer probe corresponding to the region of mRNA targeted by the

15      anti-sense (and therefore having the same sequence as the anti-sense, but not phosphorothioated) was synthesized and used to probe northern blots of RNA prepared from HAdAlAS-treated, HAdAlMM-treated and non-treated HTB-54 cells. These blots showed clearly that HAdAlAS (SEQ. ID NO:1) but not HAdAlMM (SEQ. ID NO:2) effectively reduced human adenosine receptor mRNA by >50%. This result showed that HAdAlAS (SEQ. ID NO: 1) is a good candidate for an anti-asthma drug since it depletes intracellular mRNA for the adenosine A<sub>1</sub> receptor, which is involved in asthma.

20

**Example 3: In Vivo Efficacy of A<sub>1</sub> Adenosine Receptor Anti-sense Oligonucleotides**

A fortuitous homology between the rabbit and human DNA sequences within the  
25 adenosine A<sub>1</sub> gene overlapping the initiation codon permitted the use of the phosphorothioate anti-sense oligonucleotides initially designed for use against the human adenosine A<sub>1</sub> receptor in a rabbit model.

Neonatal New Zealand white Pasteurella-free rabbits were immunized intraperitoneally within 24 hours of birth with 312 antigen units/mL house dustmite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA), mixed with 10% kaolin. Immunizations were repeated weekly for the first month and then biweekly for the next 2 months. At 3-4 months of age, eight sensitized rabbits were anesthetized and relaxed with a

mixture of ketamine hydrochloride (44 mg/kg) and acepromazine maleate (0.4 mg/kg) administered intramuscularly.

The rabbits were then laid supine in a comfortable position on a small molded, padded animal board and intubated with a 4.0-mm intratracheal tube (Mallinkrodt, Inc., Glens Falls, 5 NY). A polyethylene catheter of external diameter 2.4 mm with an attached latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiments. The intratracheal tube was attached to a heated Fleisch pneumotachograph (size 00; DOM Medical, Richmond, VA), and flow was measured using a Validyne differential pressure transducer (Model DP-45161927; Validyne 10 Engineering Corp., Northridge, CA) driven by a Gould carrier amplifier (Model 11-4113; Gould Electronic, Cleveland, OH). The esophageal balloon was attached to one side of the differential pressure transducer, and the outflow of the intratracheal tube was connected to the opposite side of the pressure transducer to allow recording of transpulmonary pressure. Flow was integrated to give a continuous tidal volume, and measurements of total lung 15 resistance (RL) and dynamic compliance (Cdyn) were calculated at isovolumetric and flow zero points, respectively, using an automated respiratory analyzer (Model 6; Buxco, Sharon, CT).

The animals were randomized and pretreatment values for PC50 were obtained on Day 1 for aerosolized adenosine. Anti-sense (HAdAlAS) or mismatched control (HAdAlMM) 20 oligonucleotides were dissolved in sterile physiological saline at a concentration of 5000  $\mu$ g (5 mg) per 1.0 ml. Animals were subsequently administered the aerosolized anti-sense or mismatch oligonucleotide via the intratracheal tube (approximately 5000  $\mu$ g in a volume of 1.0 ml), twice daily for two days. Aerosols of either saline, adenosine, or anti-sense or mismatch oligonucleotides were generated by an ultrasonic nebulizer (DeVilbiss, Somerset, 25 PA), producing aerosol droplets 80% of which were smaller than 5  $\mu$ m in diameter.

In the first arm of the experiment, four randomly selected allergic rabbits were administered anti-sense oligonucleotide and four the mismatched control oligonucleotide. On the morning of the third day, PC50 values (the concentration of aerosolized adenosine in mg/ml required to reduce the dynamic compliance of the bronchial airway 50% from the 30 baseline value) were obtained and compared to PC50 values obtained for these animals prior to exposure to oligonucleotide.

Following a 2 week interval, animals were crossed over, with those previously

administered mismatch control oligonucleotide now administered anti-sense oligonucleotide, and those previously treated with anti-sense oligonucleotide now administered mismatch control oligonucleotide. Treatment methods and measurements were identical to those employed in the first arm of the experiment. It should be noted that in six of the eight animals  
 5 treated with anti-sense oligonucleotide, adenosine-mediated bronchoconstriction could not be obtained up to the limit of solubility of adenosine, 20 mg/ml. For the purpose of calculation, PC<sub>50</sub> values for these animals were set at 20 mg/ml. The values given therefore represent a minimum figure for anti-sense effectiveness. Actual effectiveness was higher. The results of this experiment are illustrated in both Figure 1 and Table 1.

10 **Table 1:** Effect of Adenosine A<sub>1</sub> Receptor Anti-sense Oligonucleotide upon PC<sub>50</sub> Values in Asthmatic Rabbits

	Mismatch Control		A <sub>1</sub> Receptor Anti-sense Oligonucleotide	
	Pre-oligonucleotide Administration	Post-oligonucleotide Administration	Pre-oligonucleotide Administration	Post-oligonucleotide Administration
15	Administration	oligonucleotide Administration	Administration	Administration
	3.56 ± 1.02	5.16 ± 1.03	2.36 ± 0.68	>19.5 ± 0.34**

The results are presented as the mean (N = 8) ± SEM.

The significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected test.

20 \*\*Significantly different from all other groups, p < 0.01.

In both arms of the experiment, animals receiving the anti-sense oligonucleotide showed an order of magnitude increase in the dose of aerosolized adenosine required to reduce dynamic compliance of the lung by 50%. No effect of the mismatched control  
 25 oligonucleotide upon PC<sub>50</sub> values was observed. No toxicity was observed in any animal receiving either anti-sense or control inhaled oligonucleotide.

These results show clearly that the lung has exceptional potential as a target for anti-sense oligonucleotide-based therapeutic intervention in lung disease. They further show, in a model system which closely resembles human asthma, that downregulation of the adenosine  
 30 A<sub>1</sub> receptor largely eliminates adenosine-mediated bronchoconstriction in asthmatic airways. Bronchial hyperresponsiveness in the allergic rabbit model of human asthma is an excellent endpoint for anti-sense intervention since the tissues involved in this response lie near to the point of contact with aerosolized oligonucleotides, and the model closely simulates an

important human disease.

**Example 4: Specificity of Adenosine A<sub>1</sub> Receptor Anti-sense Oligonucleotide**

At the conclusion of the crossover experiment of Example 3, airway smooth muscle from all rabbits was surgically dissected and quantitatively analyzed for adenosine A<sub>1</sub> receptor number. As a control for the specificity of the anti-sense oligonucleotide, adenosine A<sub>2</sub> receptors, which should not have been affected, were also quantified.

Airway smooth muscle tissue was dissected from each rabbit and a membrane fraction prepared according to described methods (J. Kleinstein and H. Glossmann, Naunyn-Schmiedeberg's Arch. Pharmacol. 305, 191-200 (1978), with slight modifications. Crude plasma membrane preparations were stored at 70°C until the time of assay. Protein content was determined by the method of Bradford (M. Bradford, Anal. Biochem. 72, 240-254 (1976)). Frozen plasma membranes were thawed at room temperature and were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37°C to remove endogenous adenosine. The binding of [<sup>3</sup>H] DPCPX (A<sub>1</sub> receptor-specific) or [<sup>3</sup>H] 2-[p-(2-carboxyethyl)-phenethylamino]-5'-(N-ethylcarboxamido) adenosine (CGS-21680; A<sub>2</sub> receptor-specific) was measured as previously described. S. Ali et al., J. Pharmacol. Exp. Ther. 268, Am. J. Physiol 266, L271-277 (1994).

As illustrated in both Figure 2 and Table 2, animals treated with adenosine A<sub>1</sub> anti-sense oligonucleotide in the crossover experiment had a nearly 75% decrease in A<sub>1</sub> receptor number compared to controls, as assayed by specific binding of the A<sub>1</sub>-specific antagonist DPCPX. There was no change in adenosine A<sub>2</sub> receptor number, as assayed by specific binding of the A<sub>2</sub> receptor-specific agonist CGS-21680.

**Table 2:** Specificity of Action of Adenosine A<sub>1</sub> Receptor Anti-sense Oligonucleotide

	Mismatch Control Oligonucleotide	A <sub>1</sub> Anti-sense Oligonucleotide
5	<b>A<sub>1</sub>-Specific Binding</b>	1105 ± 48**
	<b>A<sub>2</sub>-Specific Binding</b>	302 ± 22
		442 ± 171

The results are presented as the mean (N = 8) ± SEM.

The significance was determined by repeated-measures analysis of variance (ANOVA),  
and Tukey's protected test.

10 \*\*Significantly different from Mismatch Control, p < 0.01.

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The foregoing examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

## CLAIMS

1. An agent, comprising an oligonucleotide which is anti-sense to a messenger RNA (mRNA) selected from the group consisting of RNAs
  - (a) complementary to DNAs selected from the group consisting of adenosine and bradykinin receptor target genes;
  - (b) complementary to intron and exon border regions of target adenosine and bradykinin receptor genes selected from the group consisting of oligonucleotide segments comprising the 5' end, 3' end and intron/exon junction between coding and non-coding regions;
  - (c) all RNA fragments selected from the group consisting of RNAs encoding adenosine and bradykinin receptors; and
  - (d) pharmaceutically acceptable salts thereof.
2. The agent of claim 1, wherein the receptor is selected from the group consisting of adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> receptors and pharmaceutically acceptable salts thereof.
3. The agent of claim 2, wherein the receptor is the adenosine A<sub>1</sub> receptor.
4. The agent of claim 2, wherein the receptor is the adenosine A<sub>2b</sub> receptor.
5. The agent of claim 2, wherein the receptor is the adenosine A<sub>3</sub> receptor.
6. The agent of claim 2, wherein the receptor is the adenosine A<sub>2a</sub> receptor.
7. The agent of claim 2, wherein the receptor is the bradykinin B<sub>2</sub> receptor.
8. The agent of claim 1, wherein the anti-sense oligonucleotide comprises at least one phosphodiester residue linking mononucleotides substituted by a residue selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, 2'-O-methyl, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino), and phosphoramidate residues.
9. The agent of claim 1, wherein the anti-sense oligonucleotide comprises about 7 to 60 mononucleotides.
10. The agent of claim 9, wherein the anti-sense oligonucleotide comprises about 10 to about 36 mononucleotides.
11. The agent of claim 10, wherein the anti-sense oligonucleotide comprises about

12 to about 21 mononucleotides.

12. The agent of claim 1, wherein the anti-sense oligonucleotide is selected from those comprising SEQ ID NO.: 7, fragments 1 to 955 thereof and fragments of SEQ. ID NO: 7 about 7 to 18 nucleotide long.

13. The agent of claim 1, wherein the anti-sense oligonucleotide is selected from those comprising SEQ ID NO.: 8, fragments 1 to 4 thereof and fragments of SEQ. ID NO: 8 about 7 to 18 nucleotide long.

14. The agent of claim 1, wherein the anti-sense oligonucleotide is selected from those comprising SEQ ID NO.: 9, fragments 1 to 4 thereof, and fragments of SEQ. ID NO: 9 about 7 to 18 nucleotide long.

15. The agent of claim 1, wherein the anti-sense oligonucleotide is selected from those comprising SEQ ID NO.: 10, fragments 1 to 5 thereof, and fragments of SEQ. ID NO: 10 about 7 to 18 nucleotide long.

16. The agent of claim 1, wherein the anti-sense oligonucleotide is operatively linked to an agent which is internalized or taken-up by living cells.

17. The agent of claim 16, wherein the substance is selected from the group consisting of transferrin, asialoglycoprotein, and streptavidin.

18. A composition, comprising  
the agent of claim 1; and  
a carrier.

19. The composition of claim 18, wherein the carrier is selected from the group consisting of gaseous, solid and liquid carriers.

20. The composition of claim 18, further comprising a substance which inactivates mRNA.

21. The composition of claim 20, wherein the substance which inactivates mRNA comprises an enzyme.

22. The composition of claim 21, wherein the enzyme comprises a ribozyme.

23. The composition of claim 18, further comprising an agent selected from the group consisting of other therapeutic compounds, provide antioxidants, flavoring agents, volatile oils, buffering agents, dispersants, surfactants, propellants and preservatives.

24. The composition of claim 18, wherein the anti-sense oligonucleotide is present in an amount of about 0.01 to about 99.99 w/w of the composition.

25. The composition of claim 24, wherein the anti-sense oligonucleotide is present in an amount of about 0.1 to about 40 w/w of the composition.
26. The composition of claim 25, wherein the anti-sense oligonucleotide is present in an amount of about 1 to about 20 w/w of the composition.
27. A pharmaceutical composition, comprising the composition of claim 18, wherein the carrier comprises a pharmaceutically or veterinarily acceptable carrier.
28. A formulation, comprising the composition of claim 18, wherein the carrier comprises a hydrophobic carrier.
29. The formulation of claim 28, wherein the carrier comprises lipid particles or vesicles.
30. The formulation of claim 29, wherein the vesicles comprise liposomes; and the particles comprise micro crystals.
31. The formulation of claim 30, wherein the vesicles comprise liposomes comprising the anti-sense oligonucleotide.
32. The formulation of claim 29, wherein the particles comprise a lipid selected from the group consisting of N-(1-[2,3-dioleyloxy] propyl)-N,N,N-trimethylammoniummethylsulfate.
33. The formulation of claim 28, comprising a respirable formulation.
34. The formulation of claim 28, comprising an aerosol.
35. A capsule or cartridge, comprising the composition of claim 18.
36. A kit, comprising
  - the composition of claim 18; and
  - instructions for its administration.
37. The kit of claim 36, further comprising
  - a delivery device; and
  - instructions for its use in the administration of the composition.
38. The kit of claim 37, wherein the delivery device comprises an inhalator which delivers metered doses of the composition.
39. The kit of claim 38, wherein
  - the inhalator comprises a nebulizer or insufflator; and
  - further comprising a piercable or openable capsule or cartridge with solid particles of the agent.

40. The kit of claim 37, wherein  
the delivery device comprises a pressurized inhaler; and  
the formulation comprises a suspension or solution of the agent.
41. The kit of claim 39, further comprising, in a separate container, an agent selected from the group consisting of other therapeutic compounds, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants, surfactants, cell internalized or up taken agents, RNA inactivating agents, antioxidants, flavoring agents, propellants and preservatives.
42. The kit of claim 41, wherein the solvent is selected from the group consisting of organic solvents and organic solvents mixed with one or more co-solvents.
43. The kit of claim 40, wherein the agent is suspended or dissolved in a solvent, or mixtures thereof.
44. The kit of claim 43, wherein  
the solvent is selected from the group consisting of chlorofluorocarbons alone or with co-solvents; and the formulation further comprises  
an agent selected from the group consisting of surfactants, antioxidants, and flavoring agents.
45. The kit of claim 37, wherein the composition is provided in a capsule or cartridge.
46. A cell, comprising the agent of claim 1.
47. A method of treating a disease or condition associated with bronchoconstriction and/or lung inflammation, comprising administering directly into the respiration of a subject in need of such treatment the agent of claim 1, comprising an anti-bronchoconstriction and/or anti-inflammation effective amount of the anti-sense oligonucleotide.
48. The method of claim 47, wherein the agent is administered directly to the subject's lungs as an aerosol of respirable particles comprising the anti-sense oligonucleotide.
49. The method of claim 47, wherein  
the disease or condition comprises inflammation; and  
the agent comprises an oligonucleotide which is anti-sense to the adenosine A<sub>2</sub> receptor mRNA.
50. The method of claim 47, wherein  
the disease or condition comprises a respiratory disease or condition; and

the agent comprises an oligonucleotide which is anti-sense to the adenosine A<sub>1</sub> receptor mRNA.

51. The method of claim 47, wherein

the disease or condition comprises a respiratory disease or condition and lung inflammation; and

the agent comprises an oligonucleotide which is anti-sense to the adenosine A<sub>2b</sub> receptor mRNA.

52. The method of claim 47, wherein

the disease or condition comprises allergy(ies); and

the agent comprises an anti-sense oligonucleotide to the adenosine A<sub>1</sub> receptor mRNA.

53. The method of claim 47, wherein

the disease or condition comprises a respiratory disease and lung inflammation; and

the agent comprises an anti-sense oligonucleotide to the adenosine A<sub>2a</sub> receptor mRNA.

54. The method of claim 47, wherein

the disease or condition comprises a respiratory disease and lung inflammation;

and

the agent comprises an anti-sense oligonucleotide to the bradykinin B<sub>2</sub> receptor.

55. The method of claim 47, wherein the subject is a mammalian subject.

56. The method of claim 47, wherein the mammalian subject is selected from the group consisting of human and non-human subjects.

57. The method of claim 56, wherein the mammalian subject is a human.

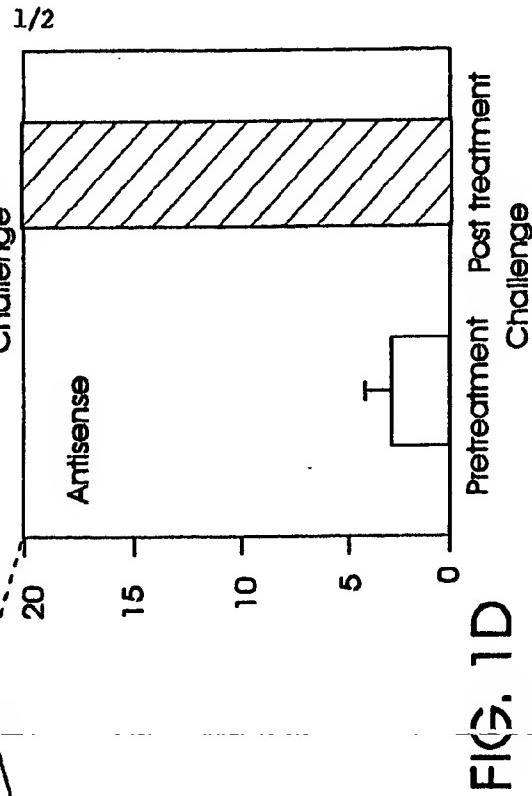
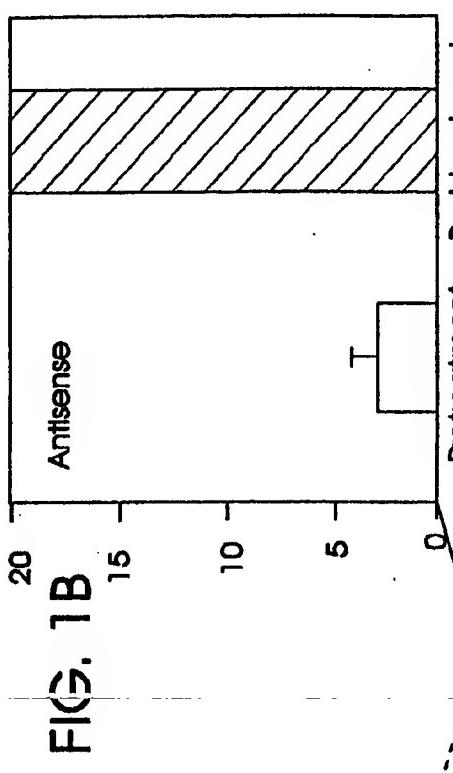
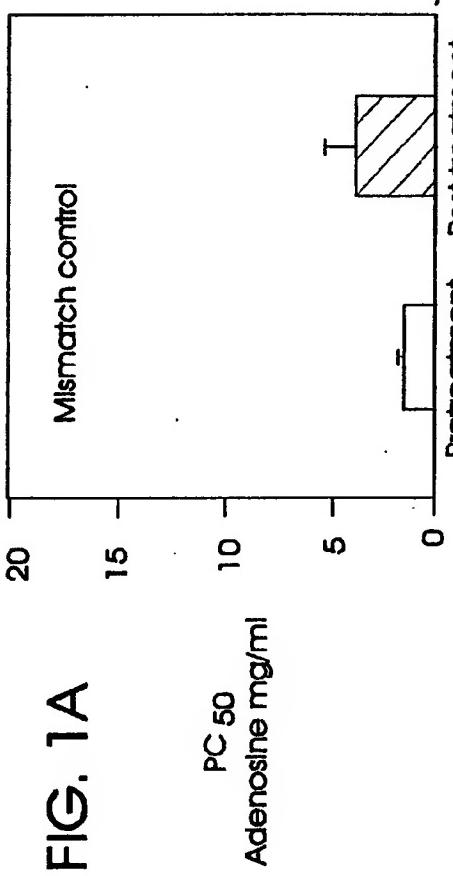
58. The method of claim 47, wherein the subject is a human.

59. The method of claim 47, wherein the receptor and the subject are of the same species.

60. The method of claim 47, wherein the receptor and the subject are of different species.

61. The method of claim 47, wherein the agent is administered as a respirable aerosol.

62. The method of claim 47, wherein  
the disease or condition is a lung disease or condition; and  
at least one of the target mRNA encodes a protein selected from the group consisting of the adenosine A<sub>1</sub> receptor, adenosine A<sub>2a</sub> receptor, adenosine A<sub>2b</sub> receptor, adenosine A<sub>3</sub> receptor, and bradykinin B<sub>2</sub> receptor.
63. The method of claim 62, wherein the disease or condition is associated with obstruction of the subject's airways and/or bronchoconstriction.
64. The method of claim 63, wherein the disease or condition is associated with asthma.
65. The method of claim 63, wherein the disease or condition is associated with inflammation.
66. The method of claim 63, wherein the disease or condition is associated with adult respiratory distress syndrome.
67. The method of claim 63, wherein the disease or condition is associated with chronic obstructive pulmonary disease.
68. The method of claim 63, wherein the disease or condition is associated with pulmonary hypertension.
69. The method of claim 63, wherein the disease or condition is associated with allergy.
70. The method of claim 63, wherein the disease or condition is associated with emphysema.
71. The method of claim 47, wherein the anti-sense oligonucleotide is administered in an amount of about 0.001 to about 150 mg/kg body weight of the subject.
72. The method of claim 71, wherein the anti-sense oligonucleotide is administered in an amount of about 0.1 to about 100 mg/kg body weight.
73. The method of claim 72, wherein the anti-sense oligonucleotide is administered in an amount of about 1 to 50 mg/kg body weight.
74. The method of claim 47, being a prophylactic method.
75. The method of claim 47, being a therapeutic method.



2/2

FIG. 2A

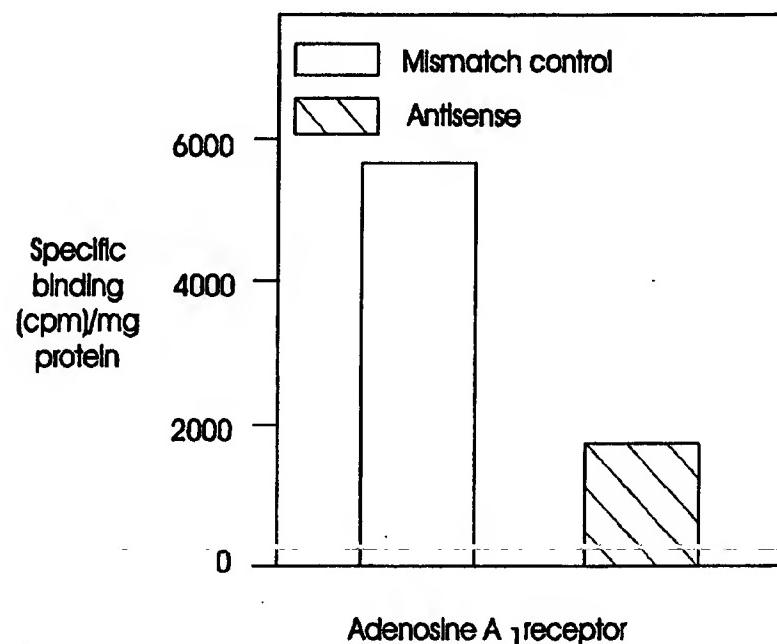
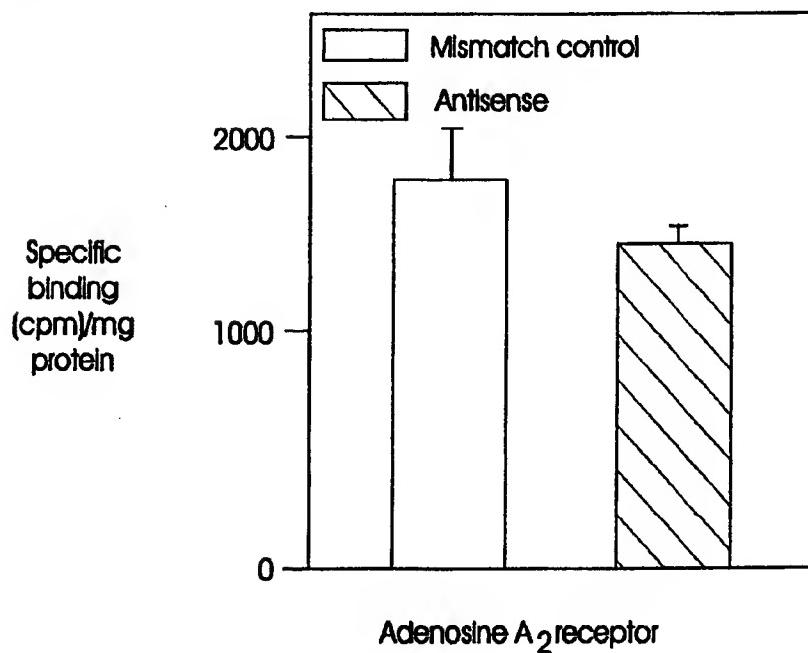


FIG. 2B



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/22017

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 48/00; C07H 21/04, 21/00; C12N 5/00, 15/63, 15/79, 15/09  
 US CL : 514/44; 435/320.1, 375, 6, 69.1, 172.3; 536/24.5, 23.1

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/44; 435/320.1, 375, 6, 69.1, 172.3, 536/24.5, 23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, BIOSIS, MEDLINE, CANCERLIT, APS  
 search terms: adenosine, antisense, oligonucleotide, asthma, bronchoconstriction

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94/02605 A1 (DUKE UNIVERSITY) 03 February 1994 (03.02.94), entire patent.	1-75
Y	US 5,245,022 A (WEIS et al.) 14 September 1993 (14.09.93), entire patent.	1-75
Y	US 5,320,962 A (STILES et al.) 14 June 1994 (14.06.94), entire patent.	1-75
Y	WO 93/25677 A1 (GARVAN INSTITUTE OF MEDICAL RESEARCH) 23 December 1993 (23.12.93), entire patent.	1-75
Y	GB 2 264 948 A (MERCK & CO. INC.) 15 September 1993 (15.09.93), entire patent.	1-75

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents	'T'	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
16 FEBRUARY 1998	20 MAR 1998

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  KAREN M. HAUDA <i>M. M. Hauda</i>
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

## INTERNATIONAL SEARCH REPORT

International application No. PCT/US97/22017
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## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ALI et al. Modification of Allergen-Induced Airway Obstruction and Bronchial Hyperresponsiveness in the Allergic Rabbit by Theophylline Aerosol. Agents Actions. 1992, Vol. 37, pages 168-170, see entire article.	1-75
Y	ALI et al. Adenosine-Induced Bronchoconstriction and Contraction of Airway Smooth Muscle from Allergic Rabbits with Late-phase Airway Obstruction: Evidence for an Inducible Adenosine A1 Receptor. J. of Pharmacology and Experimental Therapeutics. 1994, Vol. 268, No. 3, pages 1328-1334, see entire article.	1-75
Y	ALI et al. Adenosine Receptor-mediated bronchoconstriction and bronchial hyperresponsiveness in Allergic Rabbit Model. American J. of Physiology. 1994, Vol. 266, pages L271-L277, see entire document.	1-75
V	US 5,225,326 A (BRESSER et al) 06 July 1993 (06.07.93), entire patent.	1-75
Y	ALI et al. Adenosine-induced Bronchoconstriction in an Allergic Rabbit Model: Antagonism by Theophylline Aerosol. Agents Actions. 1992, Vol. 37, pages 165-167, see entire document.	1-75